Development of Cross-Coupling Routes to Macrocyclic Polyenes: The First Total Synthesis of Phacelocarpus 2-Pyrone A

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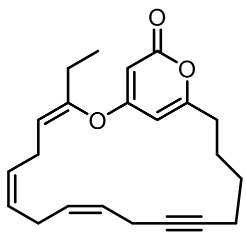
Abstract

This thesis describes the development of a synthetic approach to an unusual pyrone-containing macrocyclic natural product (**I**) isolated from the marine alga *Phacelocarpus labillardieri*. This comprises the synthesis of a simplified model system (**II**) followed by the completion of the first total synthesis of the natural product (**I**) and its suggested stereochemical reassignment, as well as studies on related palladium catalysis methodology. An overview of macrocyclic 2-pyrone natural products is given initially, along with a discussion of 2-pyrone reactivity and general macrocyclisation strategies in natural product synthesis (Chapter 1).



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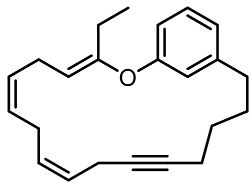
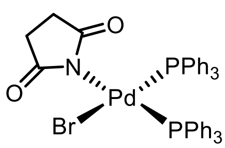


II

The synthetic route was originally developed for the synthesis of the aromatic analogue **II**, and various attempts and strategies towards this compound are described, culminating in its completion (Chapter 2). An account of the application of this strategy to the successful synthesis of the natural product (**I**) is then given, the accomplishment of which allows a reassignment of the stereochemistry around the enol ether double bond from the previously assigned *E* to *Z* in the natural compound (Chapter 3).

The remainder of the thesis focuses on two studies carried out on succinimide-based palladium complexes. The first concerns an investigation into the effect of air on the efficiency of Stille cross-coupling reactions catalysed by complex **III** (Chapter 4), and the second an examination of two novel complexes, **IV** and **V**, including their synthesis, characterisation and catalytic activity (Chapter 5).



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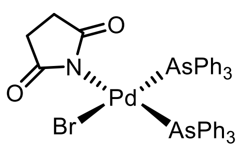

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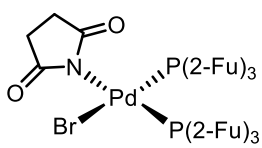

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I feel very fortunate to have had the unwavering support of my family throughout my education and especially so in these final few years; it is no exaggeration to say that it would not have been possible without my parents' help and encouragement, and I am hugely grateful to them everything they have done for me.

Finally I am deeply thankful to Jessica, who has helped me in every conceivable way, and who I am sure knows that I could never have done this without her.

Author’s Declaration

The work presented in this thesis is my own except where referenced or clearly indicated in the body of the text. The work was carried out at the University of York between October 2011 and April 2015, and has not previously been presented for an award at this or any other university.

Parts of this work have been reproduced in published papers, copies of which can be found in Appendix 1:

Ronson, T. O.; Carney, J. R.; Taylor, R. J. K.; Fairlamb, I. J. S.; AsCat and FurCat: New Pd catalysts for selective room-temperature Stille cross-couplings of benzyl chlorides with organostannanes, *Chem. Commun.*, **2015**, *51*, 3466–3469.

Ronson, T. O.; Voelkel, M. H. H.; Taylor, R. J. K.; Fairlamb, I. J. S.; Macrocyclic polyenynes: A stereoselective route to vinyl-ether-containing skipped diene systems, *Chem. Commun.*, **2015**, *51*, 8034–8036.

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Chapter 1: Introduction

1.1 Macrocycles

1.1.1 Macrocycles in Nature and Medicine

The unique characteristics of macrocycles have afforded them a prominent position in the fields of chemistry, biology and medicine.[1-2] Generally regarded as ring systems consisting of 12 or more atoms, their distinctive chemical, physical and medicinal properties set them apart from acyclic or small-ring compounds, and make them useful for a broad range of applications. Synthetic macrocycles have found use in coordination chemistry (*e.g.* [2.2.2]-cryptand (**1**), Figure 1) and form part of complex molecular architectures such as catenanes and rotaxanes (*e.g.* **2**, Figure 1).[3] Naturally occurring macrocycles are also widespread and play key roles in many biological processes: haem (**3**, Figure 1), chlorophyll and vitamin B_{12}, to name just three, all contain macrocyclic substructures.

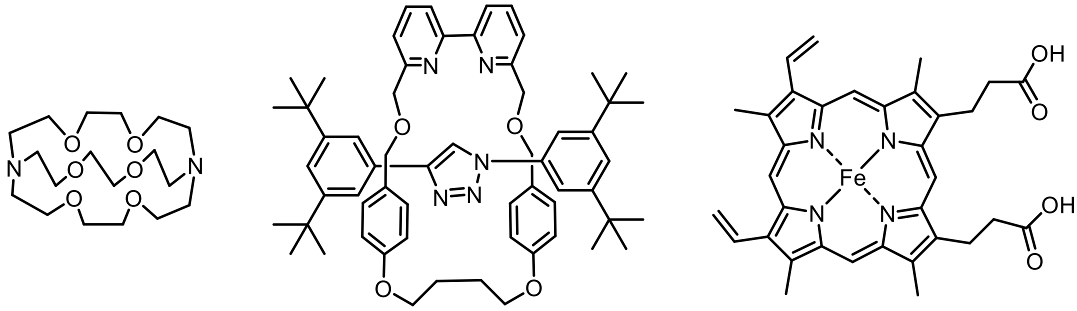


Figure 1 Examples of macrocycles with various applications: the ligand [2.2.2]-cryptand (**1**), a rotaxane (**2**) and the biological molecule haem B (**3**).

Whilst torsional, angle and transannular strains dominate the conformations of normal (5–7-membered) and medium (8–11-membered) rings, these interactions are often minimal in larger-ring compounds, giving them a considerable degree of conformational flexibility; this is combined with a certain element of constraint arising from the rotational restrictions inherent in a cyclic system. Such pre-organisation can limit the entropic penalty associated with binding to biological targets such as proteins, thus increasing potency, whilst the specific arrangement and stereochemistry of substituents on the ring can lead to very high levels of selectivity.[4] The flexibility afforded by the large ring can also allow them to shield certain functionality from the external environment, conferring enhanced solubility, good lipophilicity and the ability to penetrate cell membranes. All of these attributes mean that, despite not being classically 'drug-like',[5] macrocycles are often promising candidates for pharmaceutical agents.[6-9] As a result, macrocyclic compounds are finding increasing clinical use, for example as antibiotics, antitumour compounds, immunosuppressants and antifungals.

There are numerous examples of therapeutically active macrocyclic molecules, including natural products such as the antifungal compound amphotericin B (**4**)[10-11] and antibiotic vicenistatin (**5**);[12] natural product analogues such as the anticancer drug ixabepilone (**6**),[13] an analogue of epothilone B; or entirely synthetic compounds like pacritinib (**7**),[14] a myelofibrosis treatment currently undergoing clinical trials (Figure 2). A number of recent reviews have been published describing families of related biologically active macrocyclic natural products and their chemical synthesis.[15-18] Despite this apparent interest, macrocycles remain a somewhat under-represented structural class in the field of medicinal chemistry: at the time of writing, there were approximately 70 approved macrocyclic drugs, and historically such compounds have been derived almost exclusively from those found in nature.

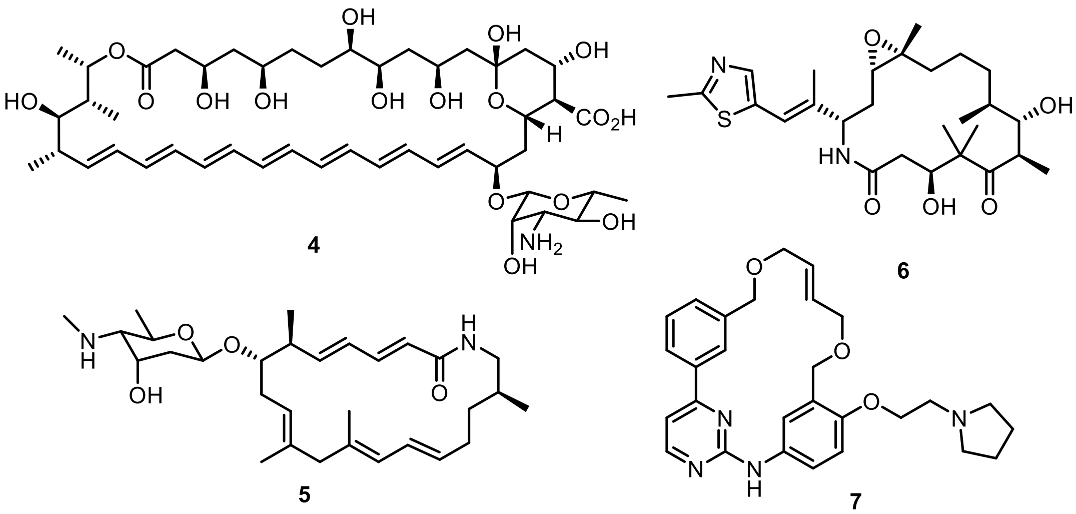


Figure 2 Examples of therapeutically active macrocycles: amphotericin B (**4**), vicenistatin (**5**), ixabepilone (**6**) and pacritinib (**7**).

There are more than 3,700 known macrocyclic natural products, constituting approximately 3% of the current total, and encompassing a vast range of sizes, functionality and biological activity.[19] Such large-ring natural products continue to pose as appealing but challenging targets to chemists, and it is this synthetic intractability which has prevented the widespread exploitation of these valuable compounds. Efficient synthetic routes to macrocycles, and in particular complex and functionality-rich macrocyclic natural products, will therefore inevitably play a vital role in the discovery of a new generation of macrocyclic drugs.

1.1.2 Synthetic Approaches to Macrocyclic Natural Products

In the cyclisation of any bifunctional compound, the main challenge to address is the competition between the desired intramolecular reaction (cyclisation) and unwanted intermolecular reactions (di-, oligo- or polymerisation). Whilst owing to the lack of strain in large ring systems the enthalpic barrier to cyclisation is small, the entropic penalty upon ring formation can make it unfavourable with respect to polymerization. The ratio between the rates of intra- and intermolecular reactions, $k_{\text{intra}}/k_{\text{inter}}$, for a given bifunctional chain is known as the effective molarity, *EM*, and has units of concentration.[20] Because the rate of intermolecular reaction is dependent on the reaction concentration, *C*, and the rate of intramolecular reaction is not, cyclisation can be favoured by lowering the reaction concentration, i.e. $C << EM$.[21-22] High dilution techniques are thus often employed despite the fact that they can lead to extended reaction times and necessitate the use of large volumes of solvent. These pitfalls can sometimes be circumvented by techniques such as slow addition of substrate (also called pseudo-high-dilution conditions) or the use of polymer-supported catalysts.[23] Metal-catalysed reactions can also benefit from a template effect by which substrate coordination to a metal atom facilitates macrocyclisation.

Historically, there have been a variety of cyclisation methods used for the synthesis of macrocyclic natural products, including radical and substitution reactions,[24] macrolactam- and macrolactonisations,[25-26] ring-closing alkene[27] and alkyne[28] metathesis reactions, olefination reactions,[29-30] Prins-type reactions[31] and Pd-catalysed reactions.[32] Of these, three major cyclisation methods have emerged as the most widely used: macrolactonisation, ring-closing alkene metathesis and Pd-catalysed cross-coupling reactions.

The prevalence and favourable biological activity of naturally occurring macrolides (macrocyclic lactones) has led to macrolactonisation being a very widely used method of macrocyclisation in natural product total synthesis. This has been achieved in a plethora of different ways using a huge range of coupling reagents which can effect esterification in a variety of fashions. Examples (Figure 3) include Yamaguchi’s reagent (**8**), cyanuric chloride (**9**), Mukaiyama’s reagent (**10**), DCC (**11**), DMC (**12**) and Shiina’s reagent (**13**).

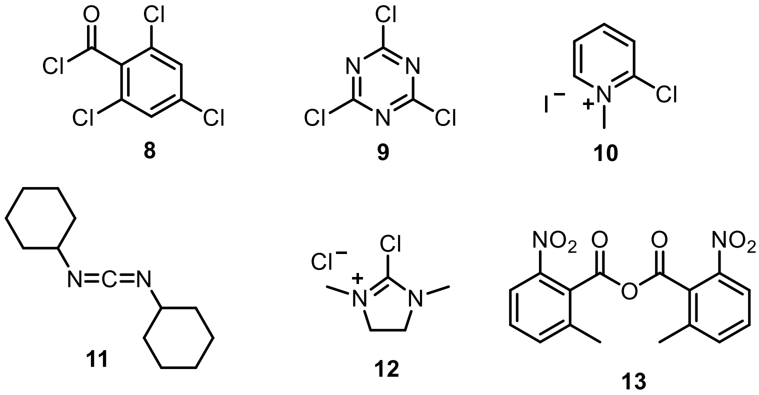
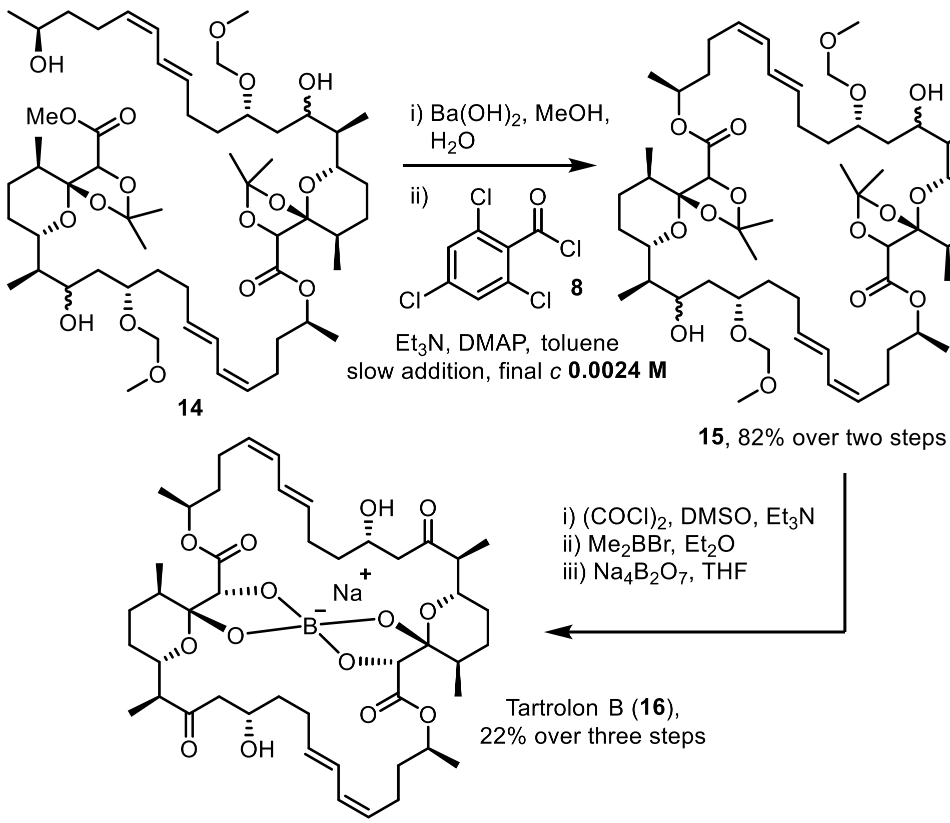


Figure 3 Examples of coupling reagents used in macrolactonisation approaches to natural products.

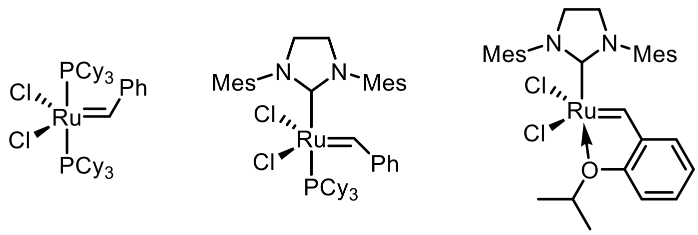
One of the more striking examples of this approach is the construction of the 42-membered ring in the unusual boron-containing natural product tartrolon B **16** (Scheme 1).[33-34] The macrocyclisation step occurs in a remarkably high yield (82% over two steps) using a Yamaguchi lactonisation. Oxidation, deprotection and reaction with $Na_2B_4O_7$ to install the boron atom then complete the first total synthesis of tartrolon B.



Scheme 1 Example of a Yamaguchi macrolactonisation in the total synthesis of tartrolon B (**16**).

Whilst this strategy has frequently been employed with great success, dimerisation is often a problem, requiring reactions to be run under high-dilution conditions, and not all substrates are compatible with the reagents employed, necessitating careful protecting-group strategies. Finally this reaction class is obviously only applicable to the synthesis of macrolides and so other methods have also needed to be developed.

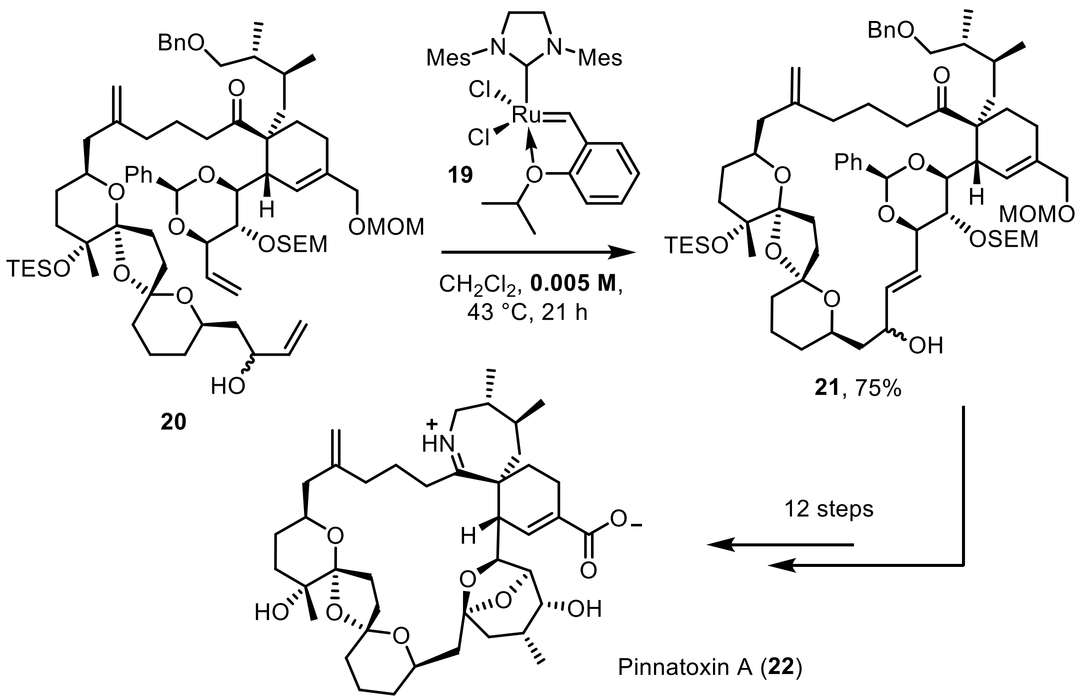
The second major macrocyclisation method in natural product total synthesis is ring-closing alkene metathesis. As in other metathesis reactions, a variety of catalysts with different catalytic activities can be employed depending on the substrate. Examples of such catalysts are given in Figure 4: Grubbs' 1st generation catalyst (**17**), Grubbs' 2nd generation catalyst (**18**) and the Hoveyda–Grubbs 2nd generation catalyst (**19**).



17 **18** **19**

Figure 4 Representative catalysts used in RCM macrocyclisation approaches to natural products.

The effectiveness of this approach has been amply demonstrated in a number of elegant total syntheses of pinnatoxin A (**22**),[35-37] a potent toxin from the shellfish *Pinna muricata* which has been responsible for a number of shellfish poisonings in East Asia. The most recent synthesis was reported by Zakarian and co-workers in 2011, who employed catalyst **19** to construct the macrocyclic core of the natural product (Scheme 2).[37]

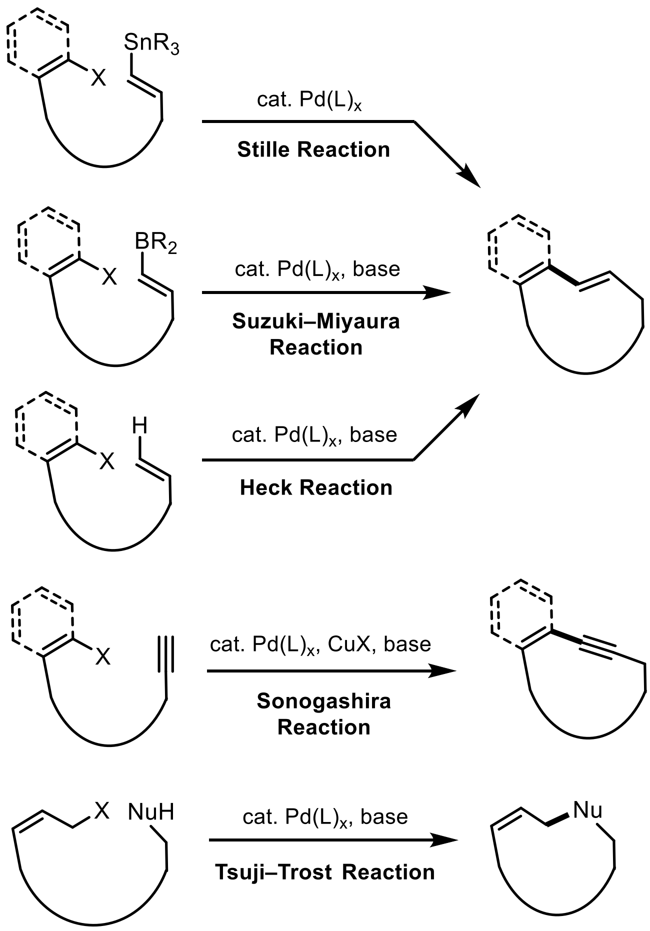


Scheme 2 Ring-closing metathesis macrocyclisation in the total synthesis of pinnatoxin A (**22**).

Whilst the substantial benefits of this strategy have led to it being widely utilised as a macrocyclisation method, it does suffer certain functional-group limitations: other double bonds present in the target compound can isomerise, migrate or even undergo metathesis themselves, leading to unwanted side-products. If the double bond resulting from the RCM is not present in the final target compound, it can be hydrogenated or transformed into numerous other groups, but this requires additional synthetic steps and potentially raises further chemoselectivity issues.

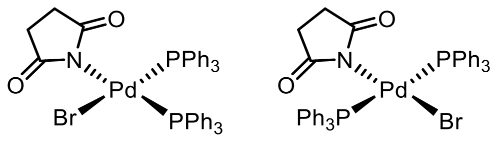
The third key reaction class is Pd-catalysed macrocyclisations. A wide array of Pd-catalysed cross-coupling reactions have in general proved themselves as invaluable tools in the total synthesis of natural products, allowing the efficient and selective formation of carbon–carbon bonds.[38] As a macrocyclisation strategy, this approach does not suffer from some of the limitations of other methods: the wide range of possible reactions means there are few specific functional-group constraints on the resulting cycle, and the mildness of many of the reactions often allows the macrocyclisation step to be performed at a late stage in the synthesis. As such, this class of reactions arguably represents one of the most promising approaches for the synthesis of new macrocycles, and the success in the previous application of this to natural product total synthesis has been reviewed in detail (see Appendix 1).[32]

The sheer diversity of these different Pd-catalysed reactions makes them attractive methods for macrocycle formation, allowing a choice of disconnections and application to a huge variety of molecules. A vast array of different cross-couplings have been developed employing a plethora of different organometallic reagents which can react with various organic halides or pseudohalides. There remain however five key reactions which have proved themselves most useful for macrocycle synthesis. These are the cross-couplings of halides, or pseudohalides, with organostannanes (Stille),[39-40] organoboron compounds (Suzuki–Miyaura),[41-42] alkenes (Heck)[43-44] or terminal alkynes (Sonogashira).[45] The coupling of a nucleophile with an allylic acetate or carbonate (Tsuji–Trost)[46-47] has also frequently been used. These reactions are summarised in Scheme 3.



Scheme 3 The main types of Pd-catalysed macrocyclisation reactions employed in the total syntheses of natural products. The precise structure of the Pd-catalyst is not given, but it is usually Pd^0, where L = $2e^-$ donor and x = 2–4.

Although there are some examples of unusual and inventive Pd-catalysed reactions employed as macrocyclisation steps in natural product total synthesis, one could argue that the full potential of Pd catalysis in this field has not yet been exploited. This is illustrated by the historical dominance of five-or-so cross coupling reactions and the reliance on a small collection of simple Pd compounds (*e.g.* $Pd(OAc)_2$, $PdCl_2(MeCN)_2$, $Pd_2dba_3{\cdot}CHCl_3$) as catalysts. A huge number of Pd catalysts are described in the literature, including many well-defined molecular complexes in addition to polymer- and solid-supported and nanoparticle-based catalysts.[48] Many of these exhibit subtle and selective reactivity which would be of great value when applied to complex and multi-functional compounds. One such case is the catalyst Pd(*N*-succ)Br(PPh_3)$_2$, **23**, the *cis*- and *trans*-isomers of which are shown in Figure 5. Complex *cis*-**23** was first reported by Serrano in 1999,[49] and can be prepared in a one-pot procedure from $Pd_2dba_3{\cdot}CHCl_3$ (see Chapter 4, section 4.3).[50] The *cis*-isomer of **23** can be isomerised to the *trans*-isomer by heating in toluene; *trans*-**23** is also currently commercially available from Sigma-Aldrich.



cis-**23** *trans*-**23**

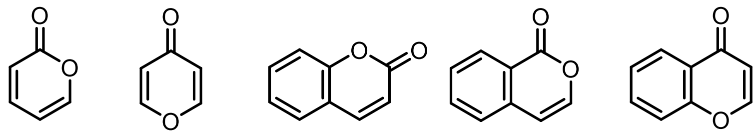
Figure 5 *cis*- and *trans*-$(Ph_3P)_2Pd$(*N*-succ)Br, **23**.

Studies by Fairlamb, Taylor and co-workers have shown these catalysts to be highly efficient in certain allylic and benzylic Suzuki–Miyaura[51-52] and Stille[50, 53-54] couplings. The reasons behind this efficacy remain unclear, but the succinimide ligand is thought to play a role, and the active catalytic species is suspected to differ in the presence and absence of trace air. These compounds have great potential for use in the total synthesis of complex natural products containing allylic or benzylic functionality, and it is the application of catalysts such as these which will allow the synthesis of new macrocycles in ever more efficient and ingenious ways.

1.2 2-Pyrones

1.2.1 Chemistry of 2-Pyrones

The 2*H*-pyran-2-one or 2-pyrone system **24** (Figure 6) possesses remarkable chemical and biological properties. It is an unsaturated cyclic six-membered lactone, possessing reactivity characteristic of an aromatic system, a 1,3-diene and a conjugated ester.[55] By convention it is numbered from the ring oxygen, with the carbonyl function occupying the C-2 position, and hence named as an α- or 2-pyrone. The related γ- or 4-pyrone **25** is named similarly, and the benzologues **26**, **27** and **28** are known as coumarin, isocoumarin and chromone respectively.[56]



24 **25** **26** **27** **28**

Figure 6 Structures of various pyrone analogues.

Unsubstituted 2-pyrone itself (**24**) is a liquid with a hay-like odour, which polymerises slowly on standing. It has distinctive spectroscopic properties, with characteristic UV absorption peaks at 216 and 289 nm,[57] a C=O IR stretch at 1720 cm^{-1},[58] and four discrete multiplets in its ^1H NMR spectrum between δ 6.38 and 7.77 (Figure 7).[59]

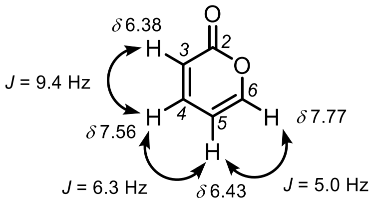
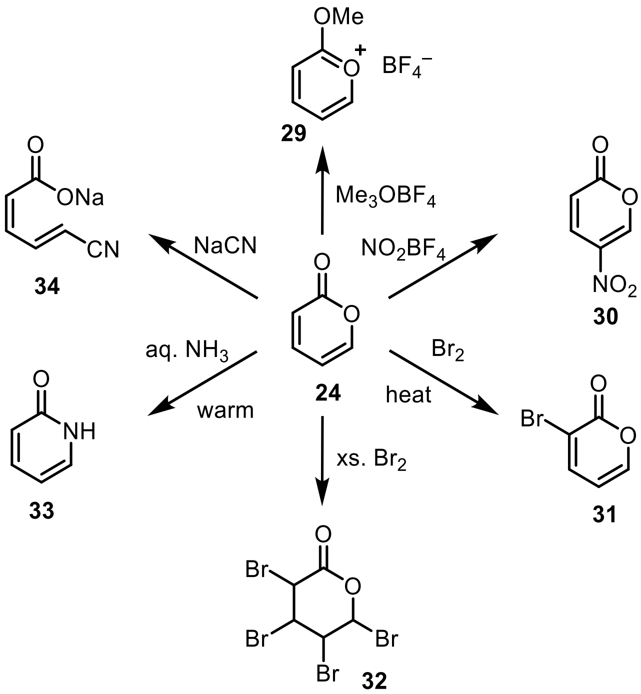


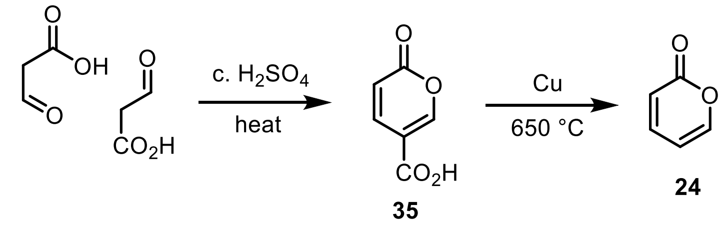
Figure 7 Numbering and ^{1}H NMR spectroscopic properties of the 2-pyrone ring system (**24**).

The pattern of nucleo- and electrophilic reactivity around the ring is similar to that of an unsaturated ester. The C-2, C-4 and C-6 positions are electron-deficient, while the C-3 and C-5 positions are relatively electron-rich, as demonstrated by reactions with electrophiles such as bromine[60] or a nitronium ion[61] (Scheme 4). Reaction with a hard electrophile such as Me_3O^+ occurs on the carbonyl oxygen, whilst the reaction with excess bromine mirrors that of a diene, resulting in the fully brominated lactone **32**. Nucleophilic attack occurs directly at the carbonyl C-2 or in a Michael fashion at C-4 or C-6, and usually results in subsequent rearrangement or ring opening, as illustrated by the reactions with aqueous ammonia or sodium cyanide,[62] to give **33** and **34** respectively.



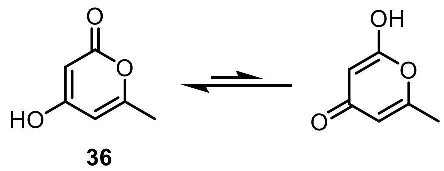
Scheme 4 Reactions of 2-pyrone **24** with a variety of nucleophiles and electrophiles.

There are numerous published methods for the synthesis of 2-pyrone rings, the most common being the classical acid-catalysed condensation of a β-ketoester with a ketone. This method is used in the synthesis of coumalic acid **35**,[63-64] which can be decarboxylated to give 2-pyrone **24** (Scheme 5).[65]



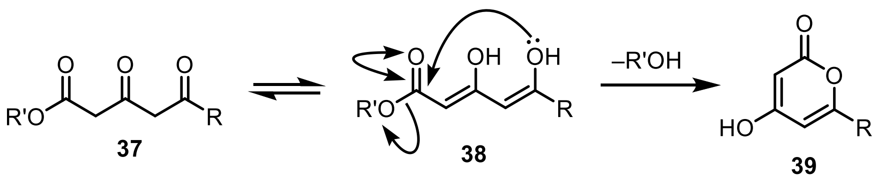
Scheme 5 Synthesis of 2-pyrone **24** *via* coumalic acid **35**.

A frequently encountered pyrone-containing substructure is 4-hydroxy-6-methyl-2-pyrone (**36**), also known as triacetic acid lactone. A cheap, commercially available and easily handled crystalline solid, this compound consists of a pyrone ring substituted with a hydroxyl group and a methyl group, and consequently can exist in two tautomeric forms: as a 2-pyrone or a 4-pyrone. It is, however, classified as a 2-pyrone ring as this tautomer is dominant (Scheme 6) as shown by comparison of the UV and IR spectra of **36** to the corresponding 4-methoxypyrones.[66]



Scheme 6 Tautomeric forms of 4-hydroxy-6-methyl-2-pyrone **36**.

6-Alkyl-4-hydroxy-2-pyrones of this type can be accessed *via* the acid- or base-catalysed intramolecular cyclisation of a β,δ-diketoester (Scheme 7).[67-68] Indeed, cyclisations of this type were reported as early as 1929,[69] and have since become a commonly used approach to the preparation of these kinds of compounds.



Scheme 7 Cyclisation of a β,δ-diketoester to form a 6-alkyl-4-hydroxy-2-pyrone (**39**).

The additional functionality on the pyrone ring in **36**, and its ready availability, make this compound an especially useful and versatile intermediate in organic synthesis.[66] In addition to the diverse reactivity of the 2-pyrone system, this molecule contains an acidic hydroxyl moiety (pK_a = 4.94[70]) and an activated methyl group. The hydroxyl group can be transformed into an abundance of different functional groups including ethers,[71] halogens,[72-73] amines[73] and sulfides.[74] The methyl group is also readily functionalised by lithiation,[75] and in the methyl ether by bromination[76] or oxidation.

1.2.2 Natural and Synthetic Bioactive 2-Pyrones

The 2-pyrone ring system is abundant in nature and can be found in a vast number of natural products from bacteria, plants and animals.[77] These 2-pyrone derivatives exhibit huge structural diversity, ranging from remarkably simple structures such as the aforementioned 4-hydroxy-6-methyl-2-pyrone **36**, which has been reported as a metabolite of various enzymes,[78] to large and complex molecules such as phellinstatin **40**, isolated in 2011 from the fungus *Phellinus linteus* (Figure 8).[79] The pyrone ring is frequently found as part of conjugated polycyclic systems (*e.g.* racemosol **41** from the leaf extract of *Mesua racemosa*),[80] and incorporated into biomolecules such as steroids (*e.g.* in bufalin **42**).[81] In addition to this structural variety, compounds containing the 2-pyrone motif also exhibit a broad biological activity including antifungal, antibiotic, cytotoxic, neurotoxic and phytotoxic effects. For example phellinstatin **40** has been shown to be a potent inhibitor of *Staphylococcus aureus* as well as posessing antibacterial activity.[79] The bioactivity of the 2-pyrone moiety is such that even the simplest pyrones show biological effects: 6-pentyl-2-pyrone **43**, a pungent compound from the soil fungus *Trichoderma viride*[82] which is also found in peach and nectarine extracts, exhibits antimicrobial activity against a variety of microorganisms.[83]

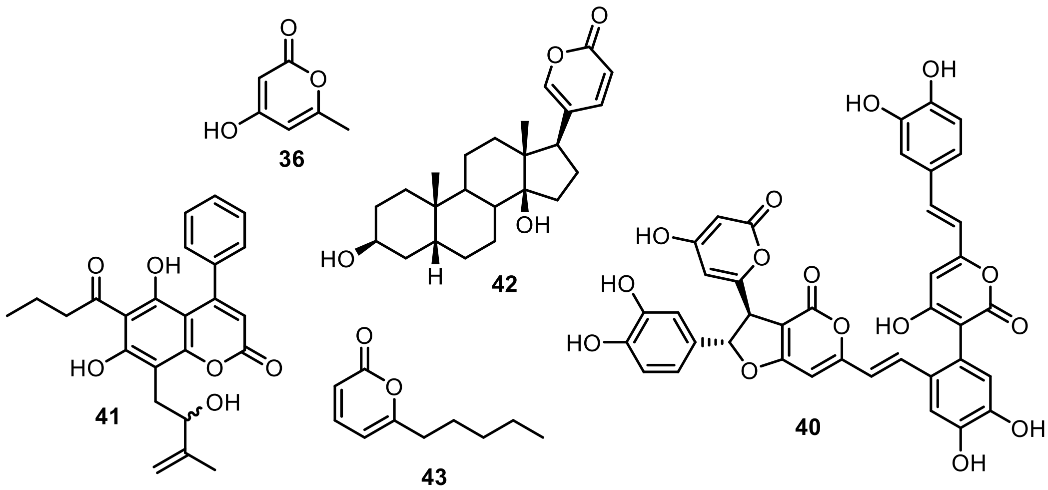


Figure 8 Examples of naturally occurring 2-pyrones.

Complementing the abundance of naturally occurring bioactive compounds, chemists have created libraries of synthetic 2-pyrones and analogues of natural products in the hope of discovering novel pharmaceutical agents. Many of these have shown favourable biological activity in tests against a variety of illnesses. For example, a screen of synthetic tricyclic 2-pyrones by Hua and co-workers found that compounds **44** and **45** (Figure 9) protected against neuron cell death from the toxicity of amyloid-β peptides, the accumulation of which is thought to lead to Alzheimer's disease.[84] A range of other tricyclic 2-pyrones such as **46** (Figure 9) exhibit potent anticancer activity comparable to anticancer drugs.[85] Another study has found that 3-alkyl-6-chloro-2-pyrones are potent inhibitors of cholesterol esterase, an enzyme which helps to absorb dietary cholesterol into the body.[86] The length of the alkyl chain at the C-6 position of the pyrone was found to be critical, and the most potent, pyrone **47**, possessed a two-methylene linker to a cyclohexyl group.

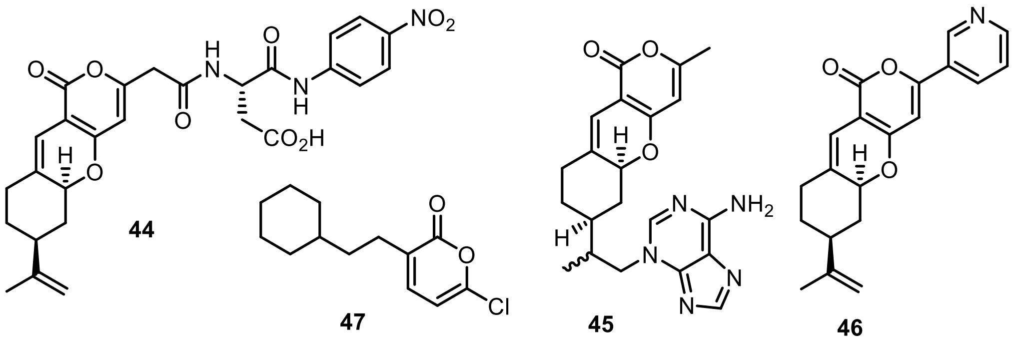


Figure 9 Examples of synthetic bioactive 2-pyrones.

The combination of the varied pharmacological profile and diverse reactivity described above has made the 2-pyrone system an important chemical entity. This has increasingly led to the use of pyrones as precursors for many synthetic compounds of therapeutic importance such as HIV protease inhibitors,[87] antimicrobials[88] and antitumour agents,[89] amongst others.[90]

1.3 Macrocyclic 2-Pyrone Natural Products

1.3.1 Isolation, Characterisation and Activity

In 1982, Blackman and co-workers reported a group of intriguing and unprecedented new compounds isolated from *Phacelocarpus labillardieri*,[91] a common red alga found abundantly around the coasts of southern Australia and New Zealand (Figure 10);[92] their interest in this species was stimulated by neuromuscular blocking activity exhibited by crude dichloromethane extracts of the alga.

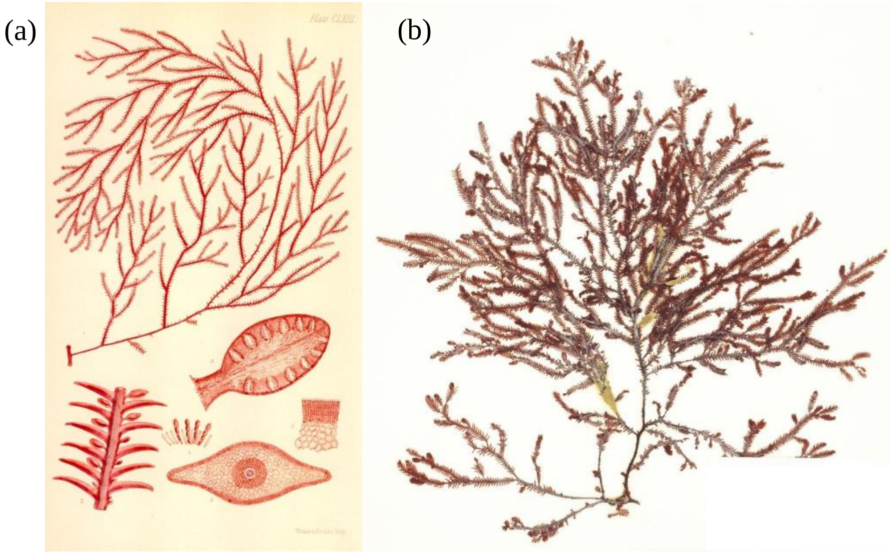


Figure 10 Images of *P. labillardieri* (a) sketch from William Harvey's *Phycologia Australica* (1860)[92] (b) photograph of sample from Tasmania (licensed under Creative Commons BY-NC-SA).[93]

Four new natural products were isolated from samples collected off the coasts of Tasmania and South Australia; the structures of the four compounds (Figure 11) were elucidated by both spectroscopic analysis and chemical degradation, and assigned as three novel macrocyclic enol ethers, each containing an embedded 4-pyrone ring (**48**, **49** and **50**), along with an acyclic 6-substituted dihydro-2-pyrone (**51**).[†] Note that the stereochemistry of the enol ether double bonds in **48** and **50** could not, at this point, be determined, but was assigned on the basis of later studies (see below).

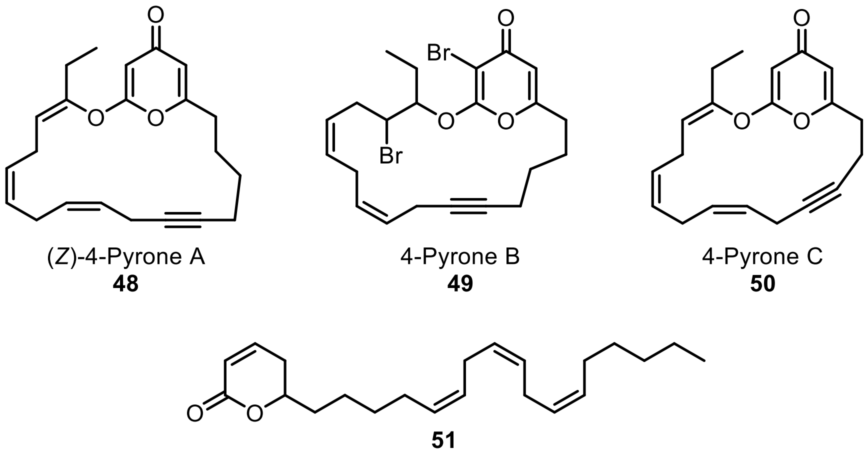


Figure 11 New natural products reported from *P. labillardieri* in 1982.

[†] In this thesis the macrocyclic compounds in this series are referred to as the 'phacelocarpus pyrones'. Isomeric compounds share the same letter (A–F) and have been named according to whether they contain a 2- or 4-pyrone ring.

Following this initial report, Fenical and co-workers reported a further four novel metabolites in 1986 from another sample of *P. labillardieri*, collected this time off the coast of Victoria, Australia (Figure 12).[94] The structures of the four compounds were assigned based on spectroscopic data and by comparison to the compounds reported previously, and were found to share many structural similarities. Compound **52** was found to be an isomer of the previously isolated **48** (Figure 11), and the lack of a ^4J allylic coupling across the enol ether bond, along with the lack of any significant nOe enhancement between these protons, implied an (*E*)-stereochemistry; this therefore suggested the assignment of a (*Z*)-stereochemistry to compound **48**. Two 2-pyrone-containing compounds were also identified: compound **53** was thought to be the 2-pyrone analogue of **52** and the dibromo compound **54** analogous to the previously identified compound **49** (Figure 11), which was also isolated from this sample.

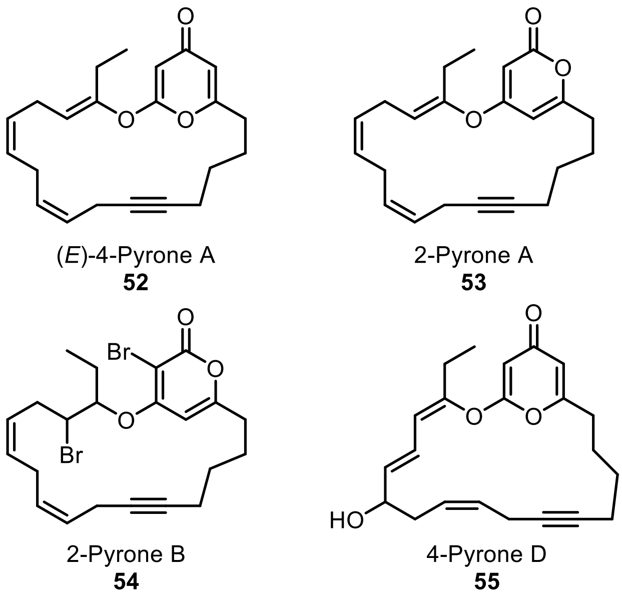
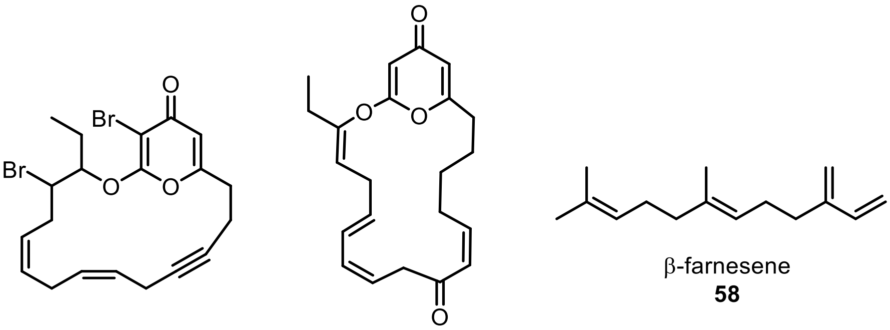


Figure 12 Further natural products from *P. labillardieri*, reported in 1986.

A subsequent study in 1990 by Blackman and co-workers on another Tasmanian collection of the algae identified a further dibrominated analogue (**56**), along with β-farnesene (**58**), a metabolite rarely found in marine organisms (Figure 13).[95] In 1995 a final, related macrocyclic 4-pyrone (**57**) was isolated, along with **50** and **52** (the stereochemistry of **50** was also determined in this study by nOe experiments), from a sample of the same algae (called by its taxonomic synonym *Phacelocarpus peperocarpus* in this study) collected in Victoria, Australia (Figure 13).[96]



4-Pyrone E
56

4-Pyrone F
57

β-farnesene
58

Figure 13 Natural products isolated in 1990 (**56** and **58**) and 1995 (**57**) from *P. labillardieri*.

In 2008, a new series of macrocyclic 2-pyrone natural products, labillarides A–K, was isolated from a collection of *P. labillardieri* from northern New Zealand (Figure 14).[97] These novel compounds bear certain structural similarities to those isolated from the Australian collections of the alga, but interestingly, none of the previously reported compounds were identified in the new samples. They were assigned as eight macrocyclic 2-pyrones (**59**–**66**), along with two macrocyclic enols (**67** and **68**), presumably biosynthetic precursors to the 2-pyrones **61** and **62**, and an acyclic 3-furanone oxylipin (**69**).

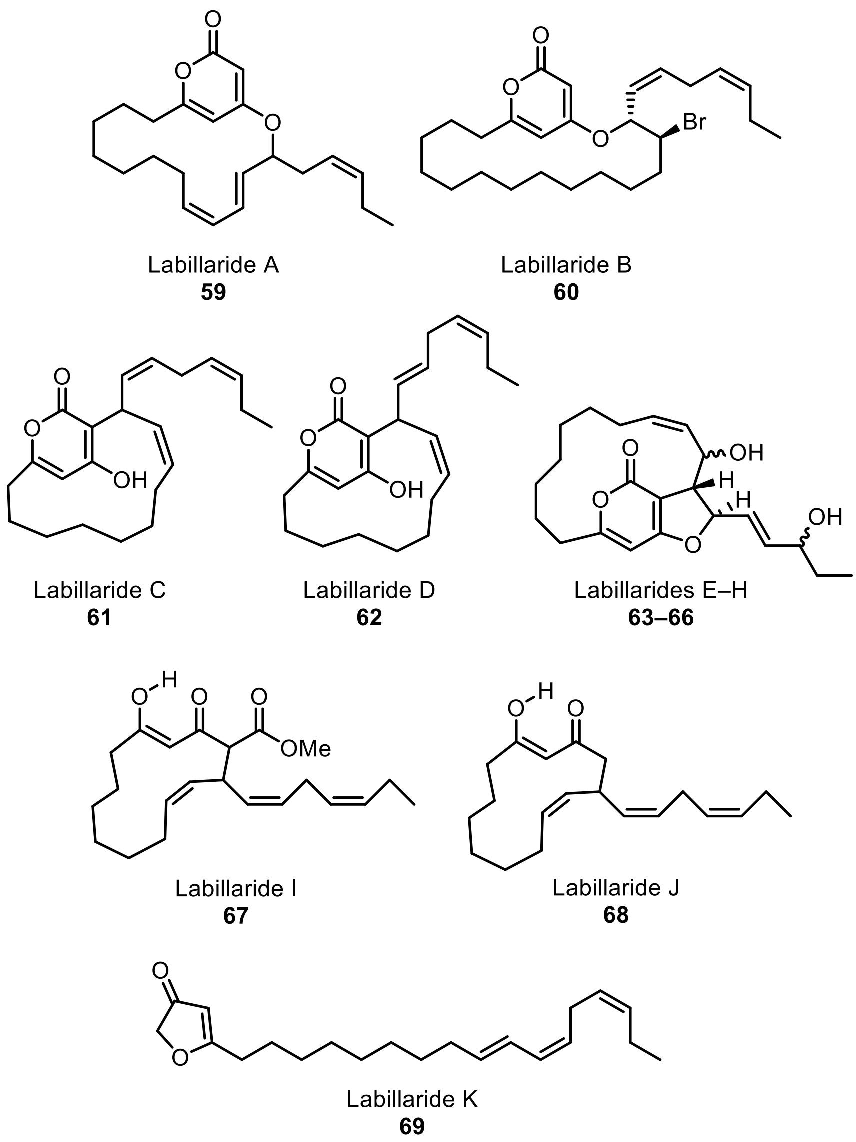


Figure 14 Labillarides A–K (**59–69**), isolated from *P*. *labillardieri* in 2008.

Finally, in 2009, two further pyrone-containing macrolides were reported as being isolated from the Fijian red alga *Neurymenia fraxinifolia* (Figure 15).[98] The structures of these two compounds, neurymenolides A (**70**) and B (**71**), are strikingly similar to that of labillaride D (**62**), differing only in the size of the macrocyclic ring and the presence of an extra alkene in the neurymenolides. This structural similarity implies a shared biosynthetic pathway, and it is interesting to note that the two species *P*. *labillardieri* and *N. fraxinifolia*, although both marine red algae, are only distantly related.

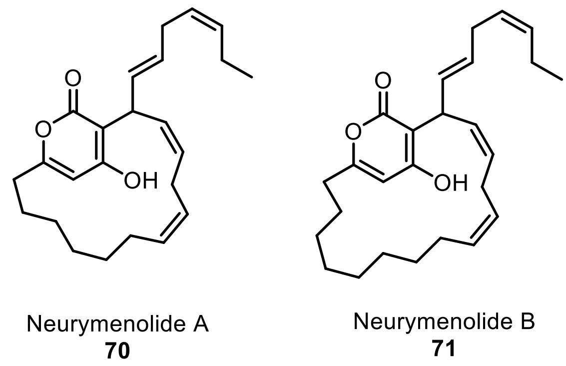
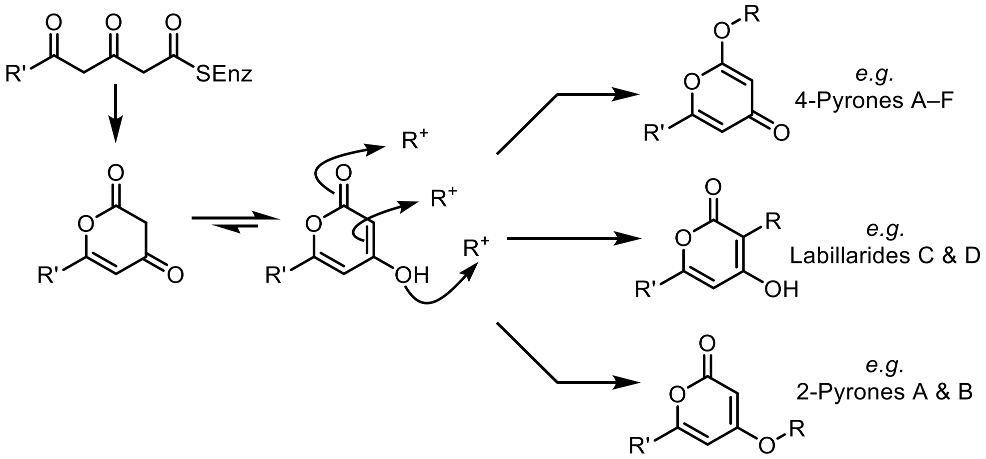


Figure 15 Neurymenolides A and B, isolated from *N. fraxinifolia* in 2009.

These final two compounds bring the total number of pyrone-containing macrocyclic natural products isolated from marine algae to 19, comprising the phacelocarpus pyrones, labillarides and neurymenolides. It is plausible that all of these natural products share similar biogenic pathways, with the pyrone moieties being formed from linear diketoacid precursors (Scheme 8). The intermediate compounds could then cyclise through either oxygen or carbon, giving rise to the range of substituted pyrones observed. It is also possible that macrocyclisation could occur prior to pyrone formation.



Scheme 8 Possible biosynthetic pathway for macrocyclic pyrones.

Many of these compounds have shown interesting biological profiles. Compound **49** has been shown to be a potent inhibitor of bee venom derived phospholipase A_2 (PLA_2) in the μM range.[99] Elevated levels of PLA_2 are associated with brain injury and neurological disorders including Alzheimer's disease.[100] Compound **48** has been demonstrated to be a potent feeding inhibitor for various marine herbivorous gastropods, and so is likely used by the algae as a defence agent against natural predators.[101] Labillarides A (**59**), B (**60**) and I (**67**) are cytotoxic, whilst labillaride C (**61**) has shown some antibacterial activity.[97] Neurymenolide A (**70**) has shown growth inhibition of drug-resistant *Staphylococcus aureus* (MRSA).[98]

1.3.2 Structural Assignment of Phacelocarpus 2-Pyrone A (53)

The phacelocarpus pyrones A and B form two isomeric sub-families as shown in Figure 16. These structurally similar compounds are 19-membered macrocycles which all share an identical portion of their macrocyclic ring (the C-5–C-17 subunit in 2-pyrone A (**53**)), differing in whether they contain a pyronyl enol ether (pyrones A) or bromination (pyrones B). Representative of this small group of unusual compounds is phacelocarpus 2-pyrone A (**53**).

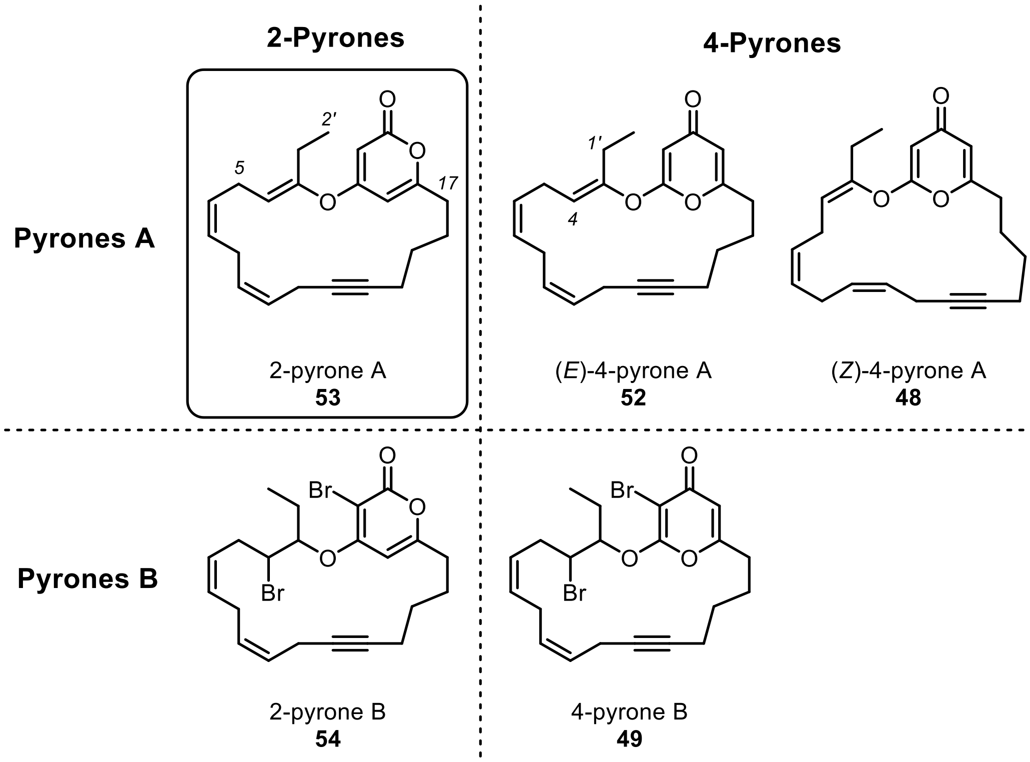
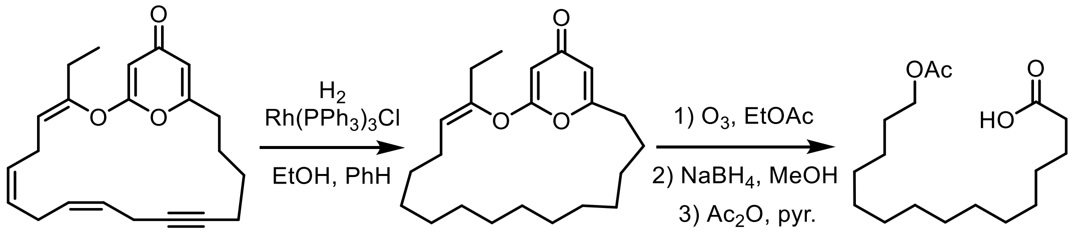


Figure 16 Classification of isomeric subgroups within the phacelocarpus pyrones.

First isolated in 1986 by Fenical and co-workers, the structure of **53** was assigned based on NMR, IR and UV spectroscopic and mass spectrometric data.[94] The presence of a 2-pyrone was indicated by a characteristic UV absorption at 282 nm, infrared bands at 1710, 1640 and 1565 cm^{-1} and ^{13}C NMR resonances at δ 167 and 169, all of which were in agreement with an authentic reference compound, 4-methoxy-6-methyl-2-pyrone. The structure of the C-2′–C-17 subunit was assigned by comparison to (*Z*)-4-pyrone A (**48**), the structure of which had been assigned previously by ^{1}H and ^{13}C NMR spectroscopic analysis and chemical degradation studies (Scheme 9).[91]



(*Z*)-4-pyrone A
48

72

73

Scheme 9 Chemical degradation studies on **48**.

The positions of the carbon–carbon triple and double bonds in **48** were determined using the ^{1}H NMR spectroscopic data. The presence of three doubly allylic methylene groups could be recognised: two triplets and one doublet with a small long range coupling. This demanded that the unsaturated bonds were homoallylic to each other and to the enol ether with the acetylene furthest around the ring. Decoupling experiments supported this assignment. The (*Z*)-geometry of the disubstituted double bonds was assumed on the basis of the small ^{1}H NMR couplings observed for the alkene protons, although exact values are not quoted and the signals are assigned as multiplets.

The later isolation of the (*E*)-isomer of **48**, (*E*)-4-pyrone A (**52**) and a subsequent nOe experiment (lack of enhancement of the C-1′ protons on irradiation of the C-4 proton in **52**, see Figure 16), suggested the respective geometries about the enol ether double bonds.[94] A *cis*-allylic coupling in **48** was also noted, which was absent in **52**, and which is known to be accentuated by a *cis* relationship. The complete structure of the aliphatic portion of compound **53**, including the stereochemistry, was thus assigned solely on the basis of a comparison to the NMR spectroscopic data for **52**. However, the match with compound **48** is also close, and since no nOe studies have been carried out directly on **53**, the compound has not been prepared synthetically, and no crystal structure has been obtained (the compound is reported to be an oil) the geometry of the trisubstituted double bond remains in doubt. Reported proton NMR spectroscopic data for compound **53** is shown in Figure 17.

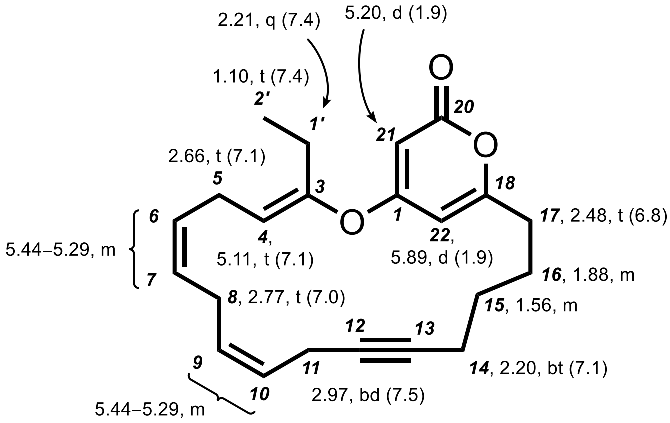
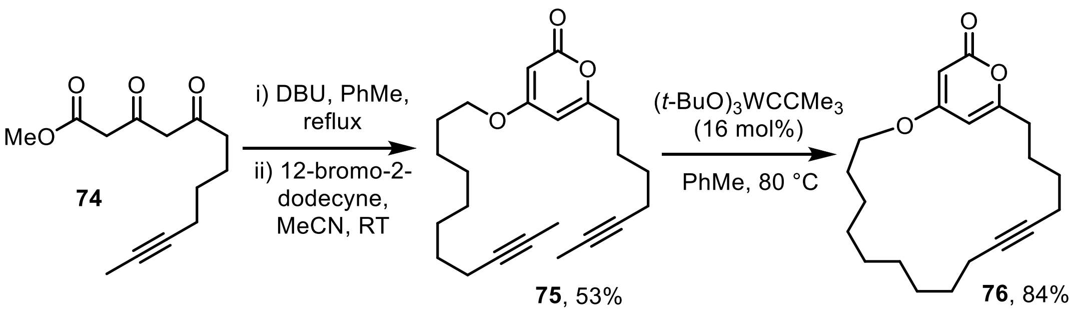


Figure 17 Numbering and reported ^{1}H NMR spectroscopic data (360 MHz, $CDCl_3$) for compound **53**.[94] Chemical shifts (in ppm) are followed by the multiplicity of the signal and the coupling constant in Hz.

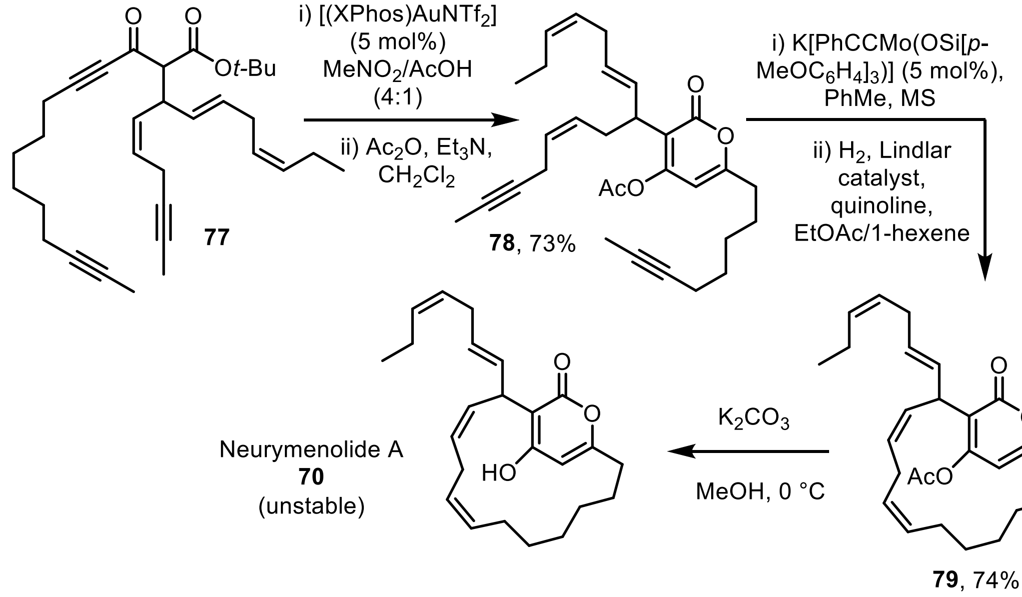
1.3.3 Synthetic Studies

Only a small number of synthetic studies towards macrocyclic pyrone-containing natural products have been carried out. In 2003, Fürstner and co-workers synthesised a model system of phacelocarpus 2-pyrone A **53**.[102] They used a base-catalysed pyrone cyclisation followed by a ring-closing alkyne metathesis (RCAM) reaction to build macrocycle **76** (Scheme 10), containing both an alkyne and an embedded 2-pyrone, but lacking the enol ether bridge or skipped (*Z*)-alkenes.



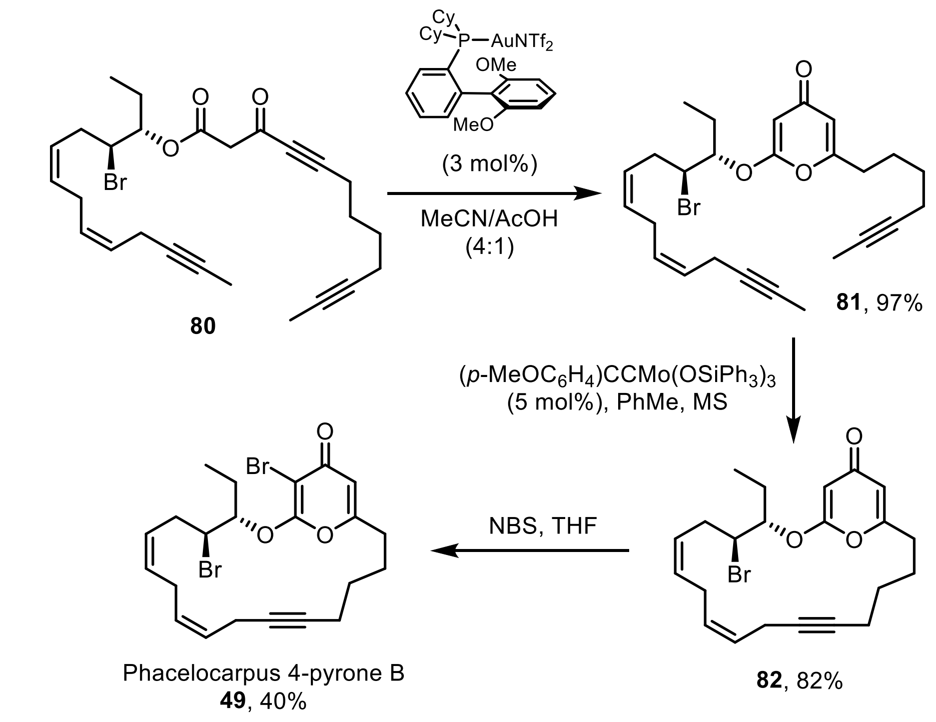
Scheme 10 Fürstner's approach to macrocycle **76**.

In 2012, Fürstner and co-workers published the first full synthesis of a macrocyclic pyrone natural product, neurymenolide A **70**.[103] They once again adopted a late-stage pyrone cyclisation, this time using gold catalysis, followed by molybdenum-catalysed RCAM as the penultimate step (Scheme 11). Partial hydrogenation of the newly formed triple bond afforded them a protected from of the natural product **70** in 13 steps and 10.8% overall yield. This could be deprotected to free neurymenolide A, confirming the correct assignment, but no yield is reported as the compound was found to be highly unstable and could not be purified. Interestingly this instability is not noted in the isolation paper, which reports purification of the natural product by both reversed-phase and normal-phase silica gel HPLC.



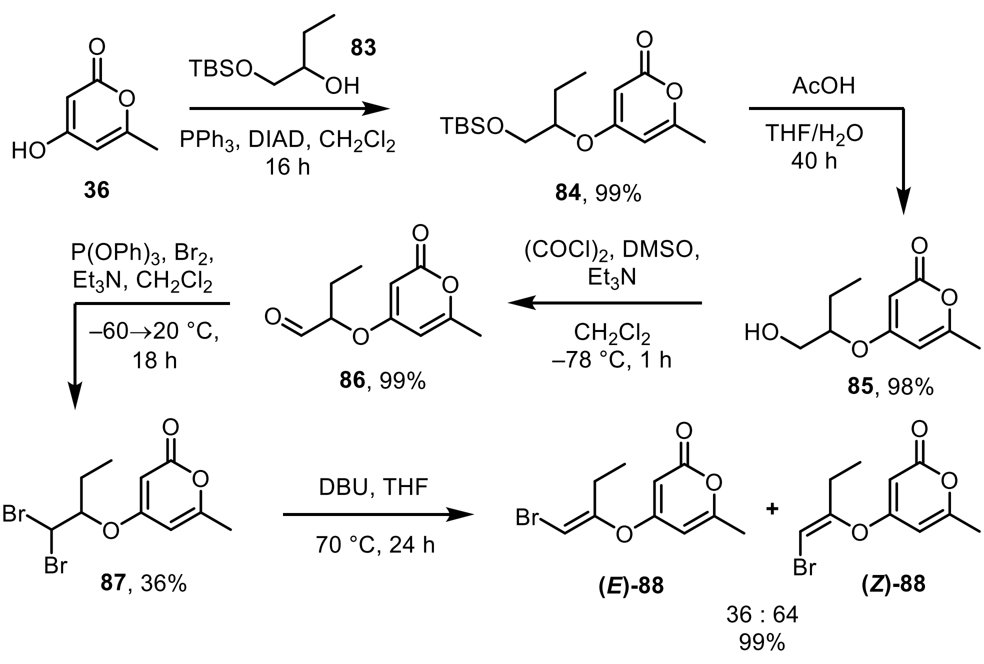
Scheme 11 Endgame synthesis towards neurymenolide A **70**.

Very recently, the group of Fürstner have completed the first total synthesis of one member of the phacelocarpus pyrones, the brominated derivative 4-pyrone B (**49**).[104] Once again, the key steps in this synthesis included gold-mediated formation of the 4-pyrone motif, followed by ring-closing alkyne metathesis to form the macrocycle (Scheme 12). A late-stage bromination on the 4-pyrone then afforded the target compound. They also synthesised the unnatural *syn* diastereomer of the natural product, allowing the confirmation of the relative stereochemistry at the two stereocentres for the first time.



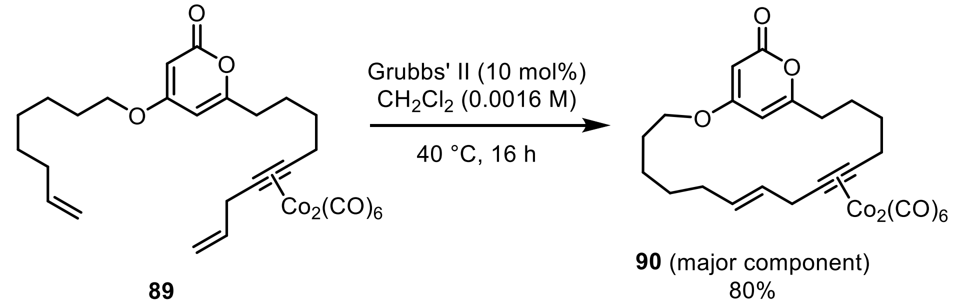
Scheme 12 Final steps of Fürstner's total synthesis of phacelocarpus 4-pyrone B **49**.

Previously in the Fairlamb and Taylor groups, significant progress has been made towards the first total synthesis of 2-pyrone **53**.[105] Dr Michael J. Burns (2006–9) established the effective use of 4-hydroxy-2-pyrones in Mitsunobu reactions and Michael additions,[106] and achieved the first synthesis of a 2-pyronyl enol ether (**88**) using an elimination strategy (Scheme 13).[107]



Scheme 13 First synthesis of a pyronylvinyl ether (**88**) by Burns.

Subsequent Suzuki cross-couplings on the vinyl bromides worked well, but the route could not be extended to the pyrone with a longer alkyl chain at C-6. A ring-closing metathesis approach to the macrocyclic ring was also investigated, and it was found that the macrocycle could be successfully accessed using this route, providing that the alkyne functionality was protected (Scheme 14). Unfortunately the RCM reaction delivered the undesired (*E*)-isomer (**90**) as the major product.



Scheme 14 RCM-based approach to macrocycle **90**.

Despite these successes, progress thus far has been hampered by the limited stability of the 2-pyrone motif under various conditions. It is therefore suggested that more success in developing the chemistry leading to the macrocyclic ring could be achieved by targeting arene model system **91** (Figure 18), in which the 2-pyrone is replaced with a benzene ring. If an efficient route could be found to compound **91**, this might potentially serve as a pathway for the synthesis of the entire family of phacelocarpus pyrones.

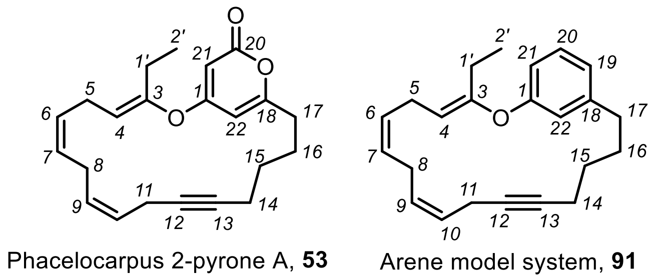


Figure 18 Structure and numbering of natural product **53**, along with aromatic model compound **91**.

1.4 Project Aims and Objectives

1.4.1 Aims

I. To complete the first total synthesis of phacelocarpus 2-pyrone A (**53**).

II. To exploit any novel or interesting observations and side reactions to develop new methodology to facilitate the synthesis of macrocyclic natural products containing 2-pyrones or skipped unsaturation.

1.4.2 Objectives

I. To identify efficient syntheses of the arylvinyl ether and skipped diene substructures, and combine these with an effective macrocyclic ring-closure, resulting in a mild and efficient synthetic route to the aromatic mimic compound **91** (Chapter 2).

II. To find an efficient and stereocontrolled synthesis of the pyronylvinyl ether motif and exploit the methodology developed in the synthesis of **91** to find an expedient route to the natural product **53** (Chapter 3).

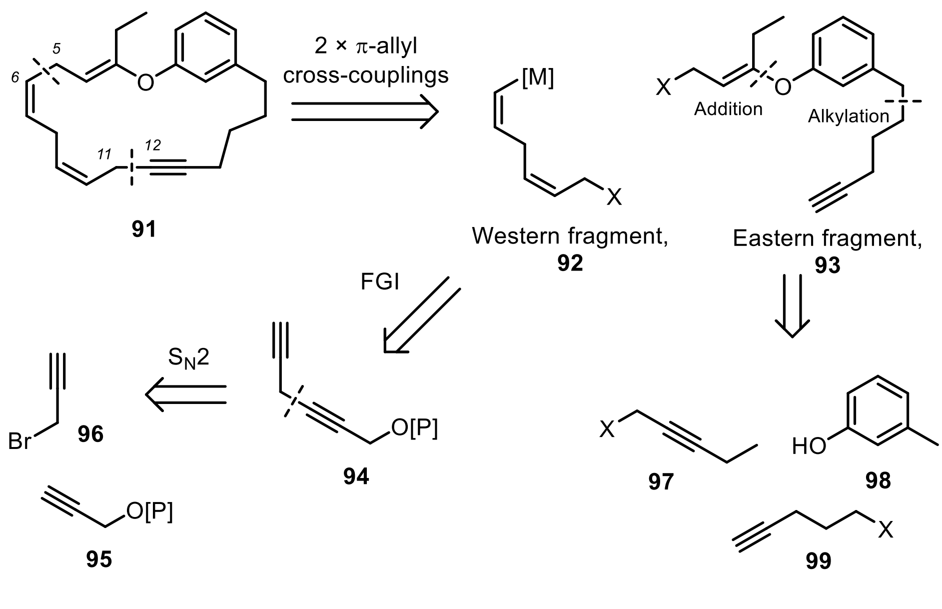
III. To investigate the reactions of succinimide-based catalysts *cis*- and *trans*-**23** in order to apply them to the synthesis of complex molecules containing skipped dienes, such as **91** and **53** (Chapter 4).

IV. To develop a new generation of succinimide-based catalysts with enhanced reactivity which could also be applied to the syntheses of **91** and **53**, and other interesting organic substrates containing skipped unsaturation (Chapter 5).

Chapter 2: Synthesis of Arene Model System

2.1 Initial Retrosynthetic Analysis

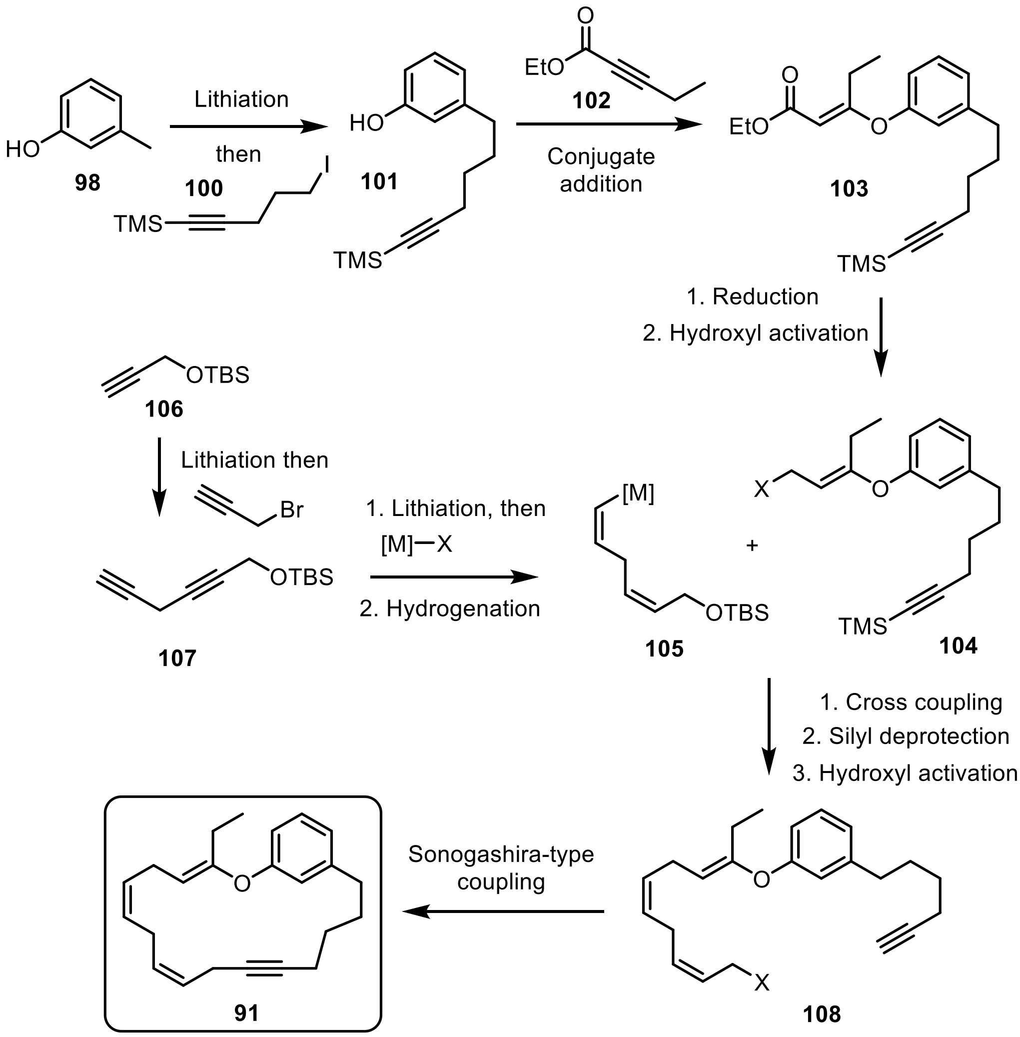
Given the arrangement of skipped unsaturated functionality present around the macrocyclic ring of compound **91**, it appeared most appropriate to focus the synthetic route around a Pd-catalysed macrocyclisation strategy, whereby a vinyl or alkynyl organometallic reagent could be coupled with an allylic electrophile. A convergent, fragment-oriented synthesis was envisaged in which the disconnections and fragments used in the synthesis of the model system **91** could also be employed in the total synthesis of the natural product (**53**). With these considerations in mind, a retrosynthetic analysis of the model system was proposed (Scheme 15), based on assembling the macrocyclic ring from two halves using Pd-catalysed cross-coupling reactions. The western fragment (**92**) would consist of a skipped diene, with two different functional handles, a nucleophilic coupling partner and an allylic electrophile; the skipped diene motif in **92** could be constructed by double hydrogenation of a skipped diyne (**94**), itself available by substitution of a terminal alkyne (**95**) with a propargylic electrophile (**96**). The eastern fragment (**93**) comprises the arylvinyl ether connected to an allylic leaving group, and a terminal alkyne tethered, via an alkyl chain, to the aromatic ring. The arylvinyl ether was anticipated to be rapidly accessed by addition of an elaborated phenol to an alkyne (**97**); the phenol itself could be assembled by alkylation of a lithiated *m*-methylphenol (**98**) with an alkyl electrophile (**99**).



Scheme 15 Retrosynthetic analysis of compound **91**.

The initially proposed forward synthesis is shown in Scheme 16. Commercially available *m*-cresol (**98**) could be alkylated with known alkyl iodide **100** and the resultant phenol

(**101**) employed in a conjugate addition with alkyne **102**. Reduction and activation would then give the required allylic electrophile (**104**). The synthesis of the western fragment begins with alkylation of known alkyne **106** with propargyl bromide; the subsequent diyne (**107**) could then be lithiated again and reacted with a metal-based electrophile. This intermediate could then be hydrogenated, affording a (*Z*,*Z*)-skipped diene (**105**). Either a Stille or a Suzuki–Miyaura coupling would be suitable to unite the two fragments; a global silyl deprotection, activation of the allylic alcohol to **108**, followed by Pd-mediated macrocyclisation reaction would then complete the synthesis. The regioselectivity of this final step should be controlled by the fact that larger rings are favoured in macrocyclisations *via* π-allyl Pd intermediates.[108]



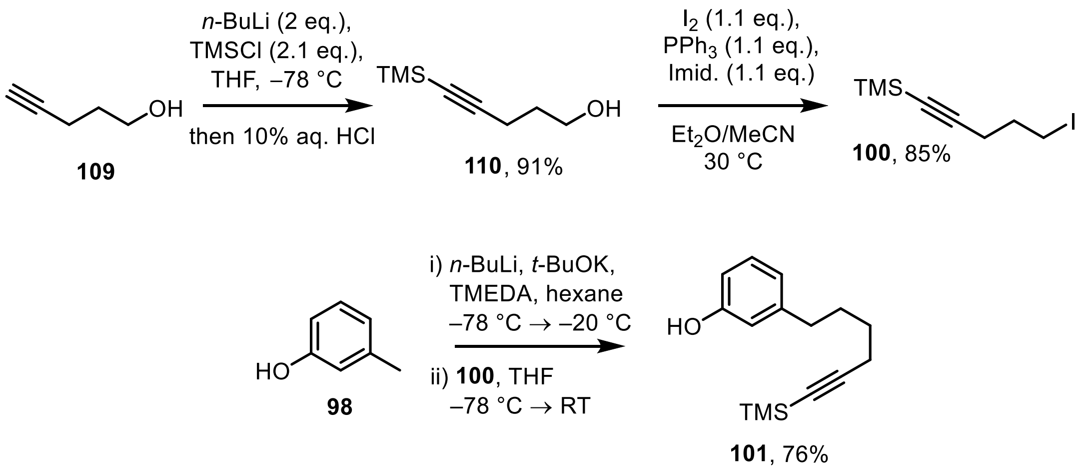
Scheme 16 Proposed forward synthesis of arene mimic **91**.

2.2 First Generation Approach

2.2.1 Construction of the Eastern Fragment

2.2.1.1 Synthesis of Phenol 101

Initial studies began with the synthesis of the alkylated phenol **101** (Scheme 17). Synthesis of the required alkylating agent, iodide **100** was achieved efficiently in two steps following a literature procedure[109] by TMS protection of the terminal alkyne of 4-pentyn-1-ol (**109**), followed by iodination under Appel-type conditions. This was then employed in an alkylation reaction whereby the dianion of *m*-cresol can be generated by using a complex base[110] formed from a combination of *n*-BuLi, *t*-BuOK and TMEDA.[111-112] Such dimetallated species then undergo reaction with electrophiles preferentially at the deprotonated methyl group, allowing selective alkylation. Pleasingly this reaction worked well, with the alkylated phenol **101** being obtained after purification in up to 76% yield, and no *O*-alkylation product being detected.

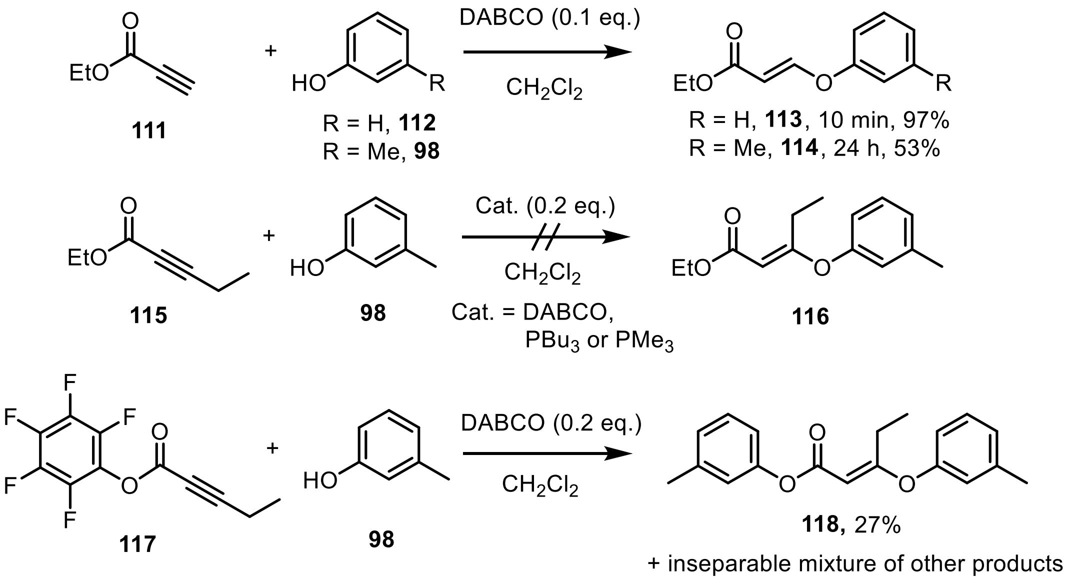


Scheme 17 Synthesis of phenol **101**.

2.2.1.2 Construction of the Arylvinyl Ether

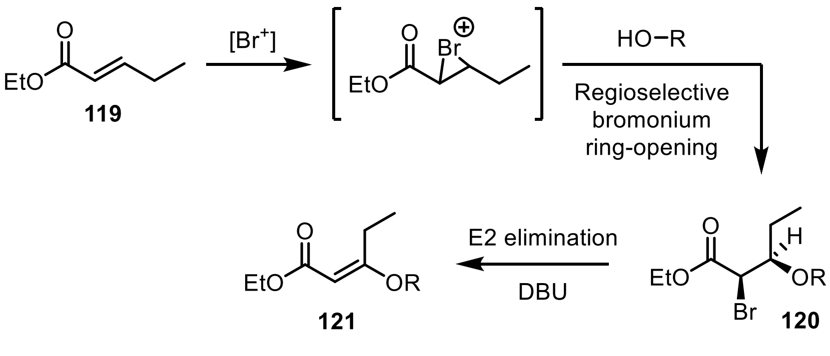
A wide variety of methods are reported in the literature for the synthesis of vinyl ethers.[113] In particular, reports have described the straightforward oxy-Michael addition of oxygen-based nucleophiles to terminal alkynoates using a nucleophilic catalyst.[114] This process was repeated employing catalytic DABCO for the reaction between ethyl propiolate (**111**) and phenol (Scheme 18), although unexpectedly, addition was rather more sluggish when *m*-cresol was used in place of phenol. This success, however, could not be repeated when an internal alkyne (**115**) was used, with either DABCO or alkyl phosphine catalysts.[115] Activation of the ester with a pentafluorophenyl group (**117**) gave modest yields of the 1,4-

conjugate addition product (**118**), but with mixtures of products and poor yields it was obvious that this approach was unfeasible.



Scheme 18 Addition attempts to various alkynoates.

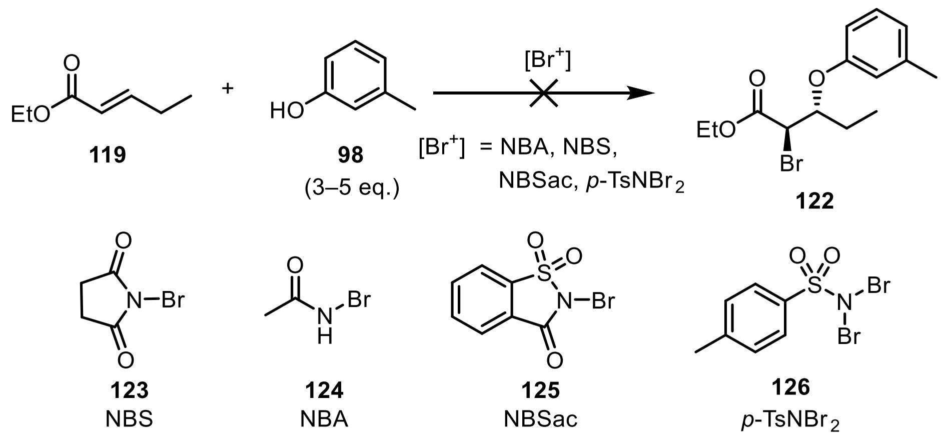
The limitations of the above reactions prompted the exploration of an E2 elimination approach, whereby the stereochemistry of the resultant double bond could be controlled by the geometry of the starting alkene; *e.g.* if the concerted elimination process was carried out on 2-bromoether **120** (Scheme 19), complete stereocontrol was anticipated in the formation of the desired vinyl ether **121**. Bromonium ions derived from α,β-unsaturated esters such as **119** are known to be trapped regioselectively by oxygen nucleophiles;[116] it was anticipated that this could be done with a nucleophile such as a phenol to access **120**.



Scheme 19 Proposed bromoetherification approach to vinyl ether.

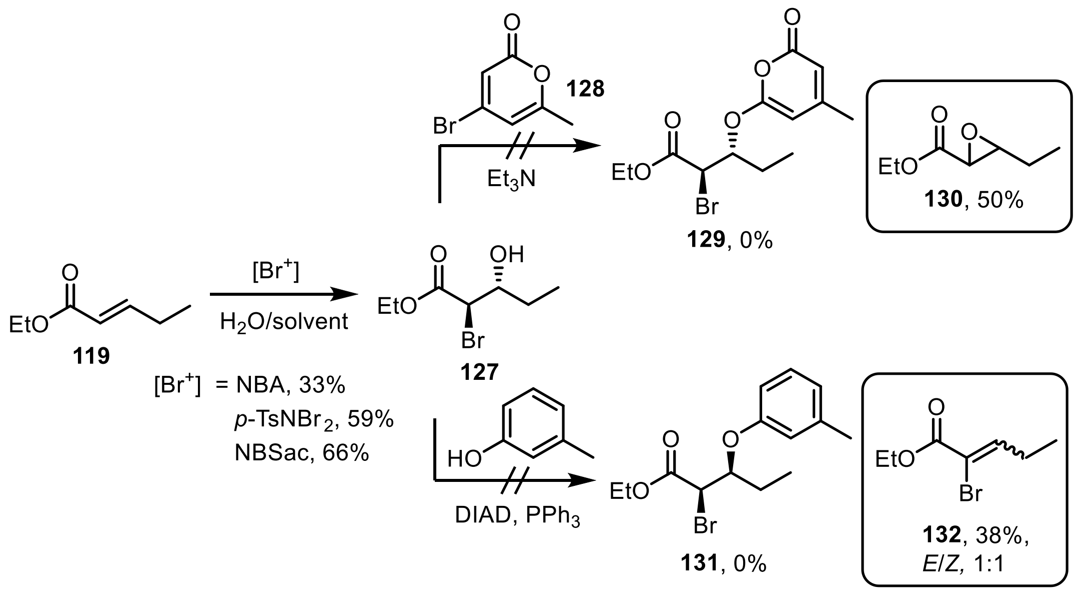
It was found that the one-pot bromination–etherification with *m*-cresol could not be performed using *N*-bromosuccinimide[117] (NBS, **123**) or *N*-bromoacetamide[118] (NBA, **124**) nor with the more electrophilic *N*-bromosaccharin[119-120] (NBSac, **125**) and *N*,*N*-dibromo-*p*-

toluenesulfonamide[116, 121] (*p*-TsNBr$_2$, **126**), with no product formation observed in any attempt (Scheme 20).



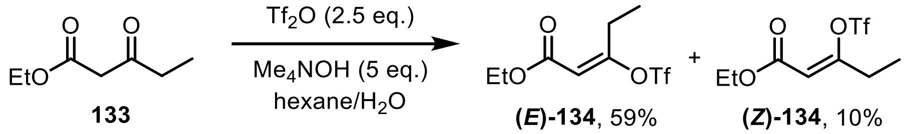
Scheme 20 One-pot bromination–etherification attempts.

In contrast, bromohydroxylation, using water as both a co-solvent and nucleophile, could be achieved with a variety of brominating agents (Scheme 21), to give bromohydrin **127**. This implies that the phenol is not a reactive enough nucleophile for the *in situ* bromonium ring-opening reaction, and perhaps that the bromonium formation is reversible. Subsequent attempts to derivatise the hydroxyl group using a Mitsunobu reaction, or electrophilic bromopyrone **128**, led only to unwanted epoxidation product **130** and E1cB elimination product **132** respectively (Scheme 21).



Scheme 21 Attempted bromohydrin derivitisations.

Numerous studies towards Pd-catalysed C–O bond formation have been described in the literature, with a number of specialised ligands and catalysts systems having been developed for the formation of biaryl ethers.[122-127] The coupling of phenols with vinyl halides or pseudohalides, however, has been much less explored.[128] Since known vinyl triflates **134** are available in one step (Scheme 22) from commercially available ethyl propionylacetate **133**,[129] it was chosen as the coupling partner for the phenol.



Scheme 22 Synthesis of vinyl triflates (*E*)- and (*Z*)-**134**.

The two stereoisomers of the enol triflate **134** could be distinguished by virtue of the presence of a *cis*-allylic coupling of $^4J_{H\text{–}H}$ = 1.3 Hz in the (*Z*)-isomer which was absent in the (*E*)-isomer (Figure 19). This is a known feature of these structural motifs, and indeed was used to support the assignment of the trisubstituted double bonds in a number of the phacelocarpus pyrone natural products (see Chapter 1).[94, 96]

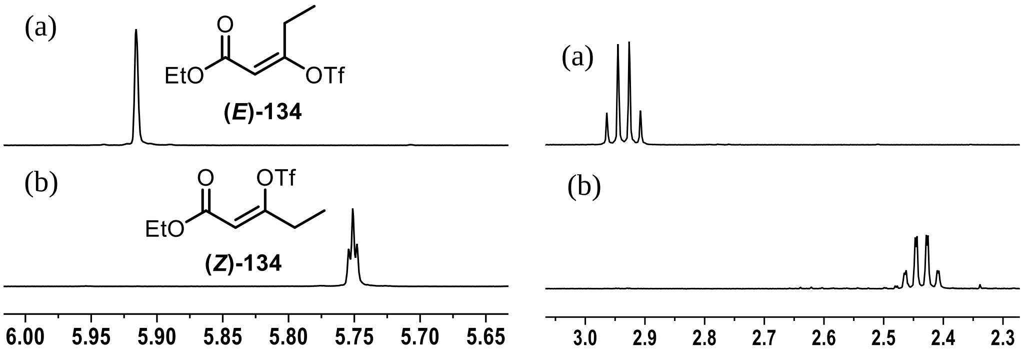
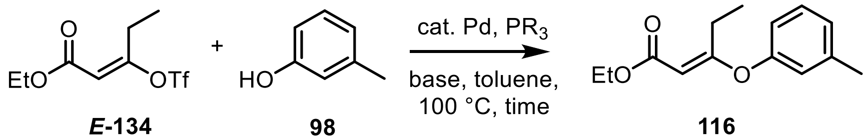


Figure 19 Expansions of the alkene and CH_2 regions of the ^{1}H NMR spectra (400 MHz, $CDCl_3$) of (a) **(*E*)-134** and (b) **(*Z*)-134**.

An initial coupling attempt of (*E*)**-134** under literature conditions[128] afforded only a modest yield of the desired product (entry 1, Table 1); this was followed by an extensive optimisation, selected examples of which are shown in Table 1 (for full details, see Appendix 2; ligands are shown in Figure 20). A combination of $Pd(OAc)_2$, X-Phos and K_3PO_4 in toluene at 100 °C was found to be the most successful, affording the product **116** cleanly in a 75% yield after only 2 h (entry 5, Table 1). Altering the Pd:ligand ratio did not affect the efficiency of the reaction, but premixing of the Pd catalyst with the phosphine ligand was found to be crucial to reaction reproducibility. Interestingly, the succinimide-containing precatalyst **23** was also found to be effective in the reaction, both with and without the addition of X-Phos (entries 7 and 8, Table 1). This highlights that PPh_3 can serve in place of X-Phos, a surprising observation given Buchwald and Hartwig's findings in earlier etherification reaction development.[122-123, 126, 130]

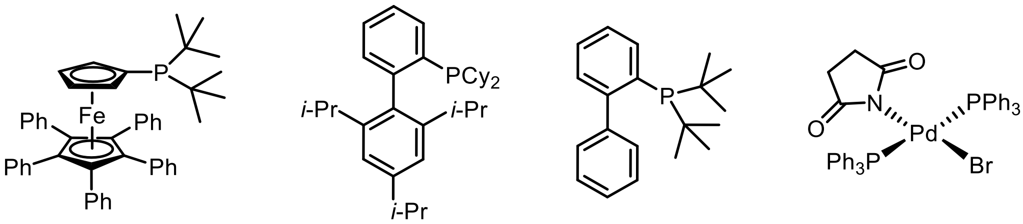
Table 1 Screening of conditions for etherification reaction.



***E*-134** **98** **116**

Entry	Catalyst [mol%]	Ligand [mol%]	Base [eq.]	Time / h	Yield[a] / %
1	$Pd_2(dba)_3$·dba [3]	JohnPhos [9]	NaO*t*-Bu [1.5]	24	19
2	$Pd(OAc)_2$ [5]	JohnPhos [5]	K_3PO_4 [2]	24	38
3	$Pd(OAc)_2$ [5]	Q-Phos [5]	K_3PO_4 [2]	24	56
4	$Pd(OAc)_2$ [5]	X-Phos [5]	K_3PO_4 [2]	24	75
5	**$Pd(OAc)_2$ [2.5]**	**X-Phos [5]**	**K_3PO_4 [2]**	**2**	**75**
6	$Pd(OAc)_2$ [2.5]	X-Phos [5]	K_3PO_4 [2]	2	61[b]
7	*trans*-**23** [2.5]	X-Phos [5]	K_3PO_4 [2]	2	60[b]
8	*trans*-**23** [2.5]	-	K_3PO_4 [2]	1.5	55[b]

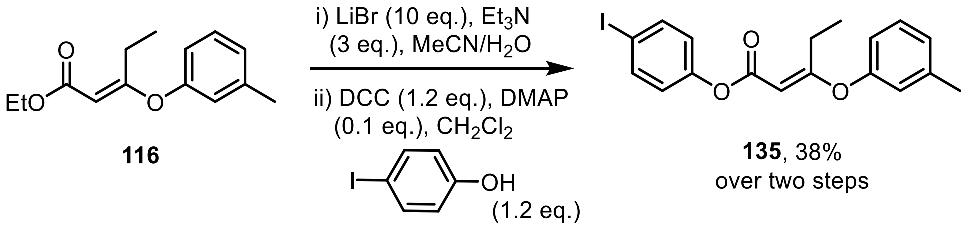
[a]Yield of isolated product following column chromatography. [b]Reaction carried out in DMF.



Q-Phos X-Phos JohnPhos *trans*-**23**

Figure 20 Structures of phosphines and catalysts employed in etherification reactions.

As with the starting enol triflate (*E*)-**134**, the compound **116** lacked an allylic coupling between the alkene proton and methylene group, implying that the (*E*)-stereochemistry had been retained. However, in order to get conclusive evidence of the stereochemistry, it was desirable to obtain a crystal suitable for analysis by X-ray diffraction. To facilitate the growing of a single crystal, a large atom was introduced by replacing the ethyl group on the ester with an aryl iodide (Scheme 23). Mild ester hydrolysis conditions were employed to avoid disrupting the enol ether linkage,[131] although in this system the reaction was sluggish, resulting in a low overall yield for the transesterfication process. Compound **135** showed comparable NMR spectroscopic characteristics to ethyl ester **116**.



Scheme 23 Synthesis of aryl ester **135**.

The crystal structure of **135** (as solved by single crystal X-ray diffraction methods) is shown below, and confirms the expected (*E*)-stereochemistry of the double bond. The packing of the unit cell revealed π-stacking and an interesting edge interaction between the iodine atom and the phenyl ring (Figure 21, see Appendix 3 for full diffraction data).

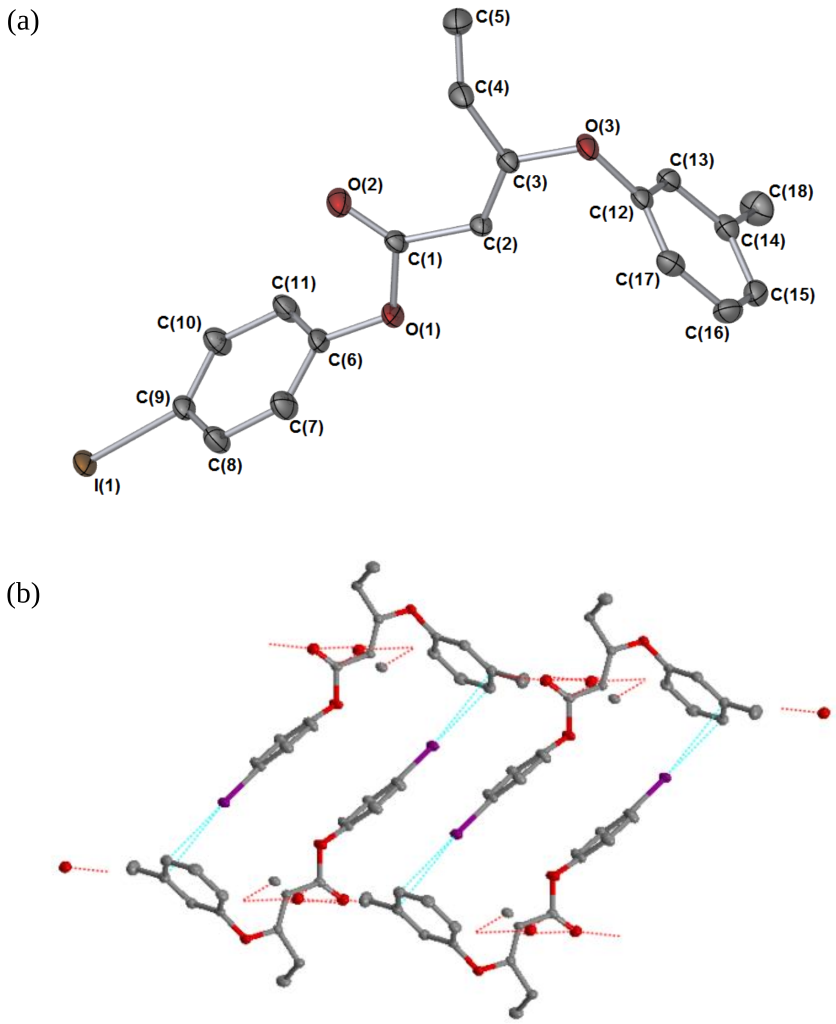
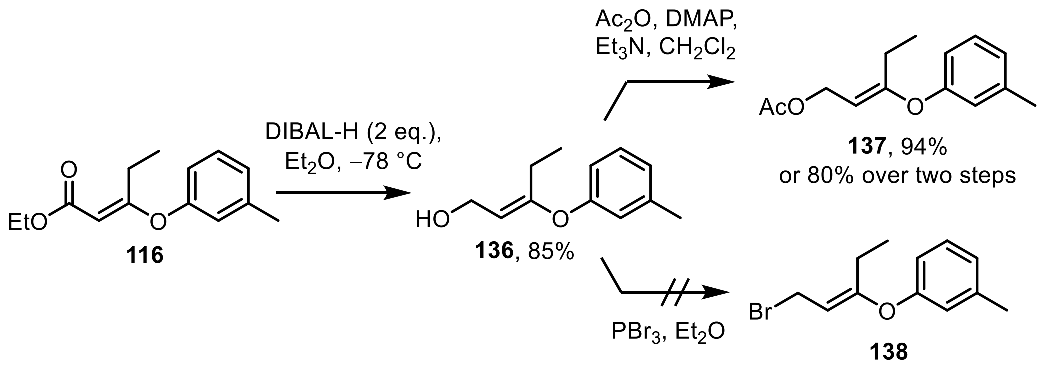


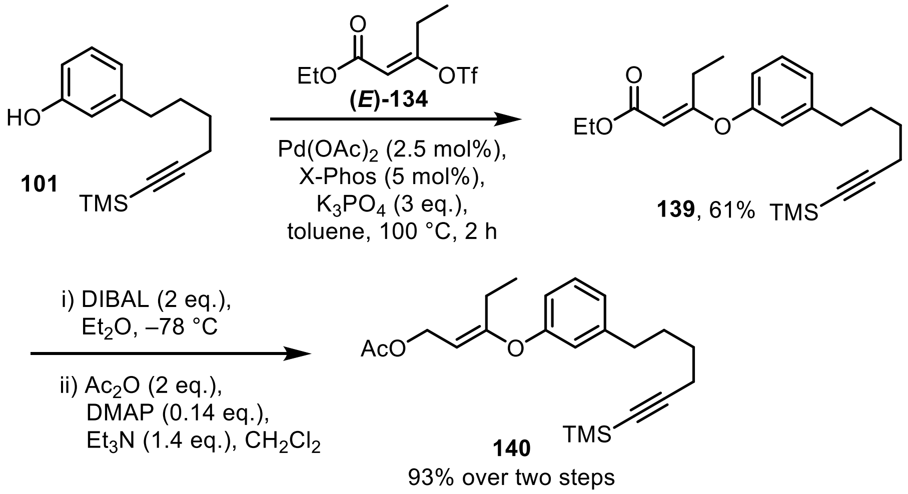
Figure 21 (a) Crystal structure of compound **135**, confirming its *E*-stereochemistry; (b) packing in the unit cell of **135**, showing an interaction between the iodine atom and aromatic ring (in blue).

With the stereochemistry of ester **116** confirmed, reduction using DIBAL-H proceeded efficiently in 85% yield (Scheme 24). The resulting allylic alcohol **136** could be readily acetylated to acetate **137**, but an attempt to generate an allylic bromide **138** by reaction with PBr_3 led to decomposition. The reduction–acetylation sequence could also be carried out without purification of the intermediate alcohol, giving an 80% yield over the two steps.



Scheme 24 Reduction and acetylation of ester **116**.

With an efficient synthesis of the desired enol ether motif in hand, the synthetic route was applied to the alkylated phenol **101**; thus acetate **140** could be accessed efficiently in 35% overall yield over six steps from 4-pentyn-1-ol **109** (Scheme 25).

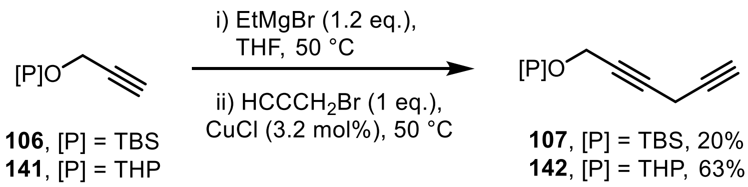


Scheme 25 Synthesis of allylic acetate **140** from phenol **101**.

2.2.2 Construction of the Western Fragment

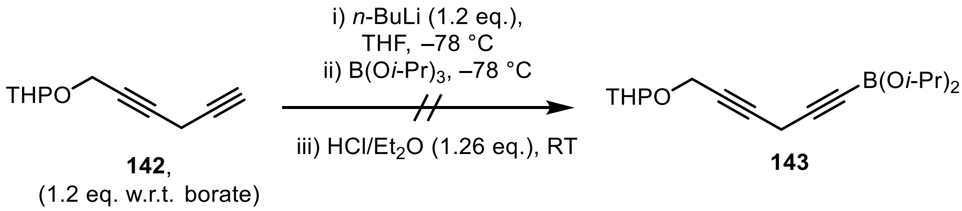
With an efficient route to the eastern half of the target molecule established, efforts were directed towards the synthesis of skipped diene fragment **105**. The initial target was a vinyl boron compound, in anticipation of using a Suzuki–Miyaura coupling to join the western and eastern fragments. In contrast to (*E*)-vinyl boronates, which are synthesised straightforwardly by the *cis*-hydroboration of terminal alkynes, there is no general method for the synthesis of (*Z*)-vinyl boronate reagents. The presence of two (*Z*)-alkenes in the molecule prompted the exploration of a hydrogenation approach, whereby a skipped diyne capped with an alkynylboronate would be prepared, and both alkynes simultaneously reduced in a Lindlar-type hydrogenation reaction. The preparation and hydrogenation of alkynylboronate esters as a route to (*Z*)-vinyl boronates was developed by Brown and co-workers in the late 1980s.[132-133]

The skipped 1,4-diyne could be assembled by the Cu-catalysed coupling of a Grignard reagent derived from a protected propargyl alcohol with propargyl bromide.[134] The use of a TBS protecting group was found to be problematic, as separation of the diyne product **107** from the remaining starting alkyne (**106**) was extremely difficult; the most successful attempt resulted in only 20% isolated yield. The purification was further complicated by the diyne's limited stability to air and silica gel. Switching to a THP protecting group resulted in easier separation and the yield of diyne **142** rose to an acceptable 63%, following column chromatography on silica gel (Scheme 26).



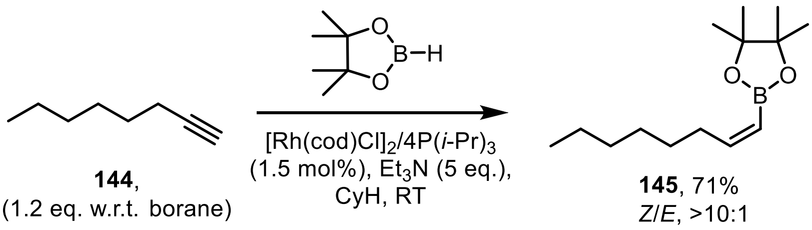
Scheme 26 Preparation of diynes **107** and **142**.

Unfortunately the subsequent synthesis of the alkynylboronate ester **143** failed, resulting only in partial deprotection of the starting material and no product was observed (Scheme 27).



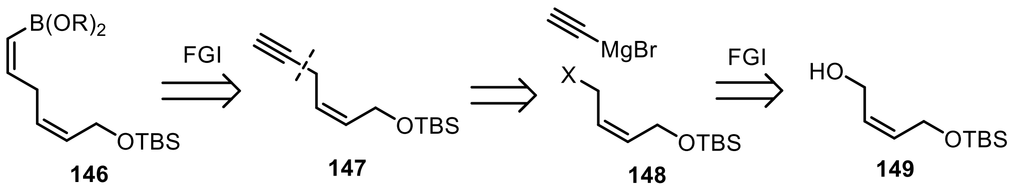
Scheme 27 Attempted borylation of terminal alkyne **142**.

The next synthetic approach examined was inspired by a report from Miyaura and co-workers, who described a formal *trans*-hydroboration of terminal alkynes with catechol- or pinacol-borane catalysed by Rh^{I} (Scheme 28).[135] The reaction proceeds under mild conditions with excellent (*Z*)-selectivity.



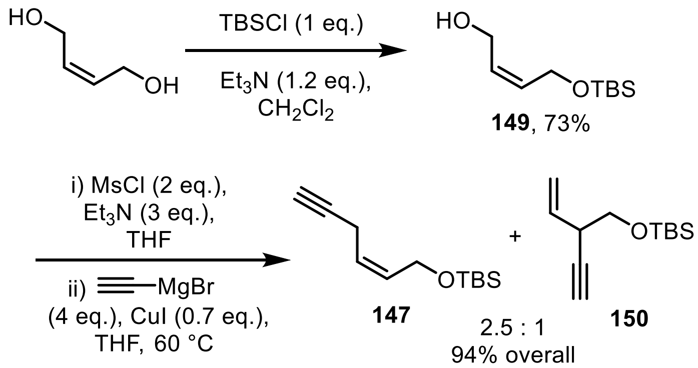
Scheme 28 Miyaura and co-workers' *trans*-hydroboration.[135]

It was decided that this approach merited investigation and a revised retrosynthetic analysis was proposed. It was thought that the simple skipped eneyne starting material could be easily accessed from allylic alcohol **149** (Scheme 29).



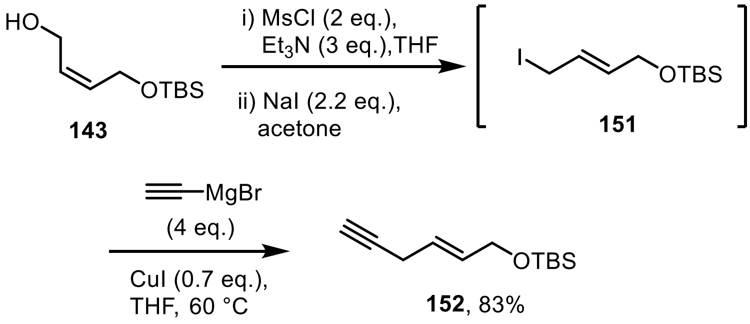
Scheme 29 Revised retrosynthetic analysis of vinyl boronate **146**.

Mono-protected alcohol **149** was obtained straightforwardly from the starting diol; an initial yield of 44% was increased to 73% by adding the TBSCl silylating agent dropwise in solution *via* syringe pump over 45 min (Scheme 30). The alkyne fragment was anticipated to be introduced by activation of the alcohol moiety followed by reaction with commercially available ethynylmagnesium bromide. Alcohol **149** was treated with mesyl chloride under standard conditions, and reaction of the resulting crude mesylate with the Grignard reagent led to the formation of an almost inseparable mixture of regioisomers **147** and **150**, arising from competing S_N2 and S_N2' substitutions (Scheme 30).



Scheme 30 Mono-protection, activation and substitution of butenediol giving a mixture of regioisomers.

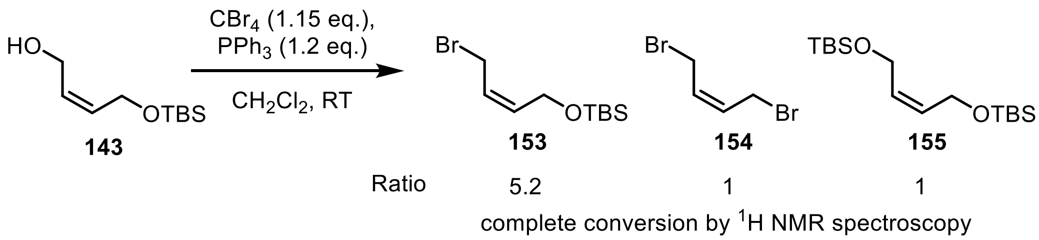
An attempt to change the leaving group to an iodide, by reaction of the mesylate with sodium iodide resulted in complete conversion into the (*E*)-alkene **151**, which was not isolated but reacted directly with the Grignard reagent (Scheme 31). Interestingly, reaction proceeded cleanly to afford the skipped enyne **152**, with no S_N2' product detected.



Scheme 31 Attempted syntheses of alkyne **152**.

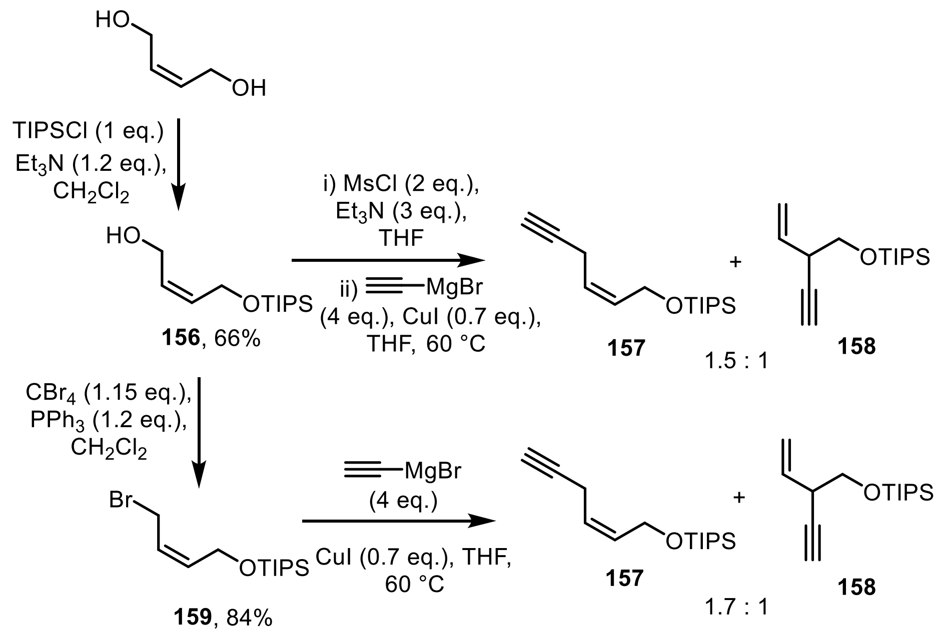
Attempts to avoid the isomerisation by lowering the temperature of the substitution reaction simply resulted in the slower formation of **152**. Alternative approaches using Appel-type reactions[136] also gave the (*E*)-isomer. A search of the literature revealed very few examples of *cis*-allylic iodides; rapid isomerisation is frequently reported.[137-138] It was postulated that the corresponding bromide might serve as a suitable alternative given the greater stability of allylic bromides.

Attempts to convert alcohol **143** directly into the corresponding allylic bromide using CBr_4 and PPh_3, under literature conditions,[139] led to side reactions in which the TBS group appeared to be undergoing an intermolecular transfer reaction; this resulted in inseparable mixtures of product **153** with the corresponding bis-bromide **154** and bis-silyl ether **155** (Scheme 32). These unwanted side products could not be avoided by altering either the bromine source, phosphine or solvent.



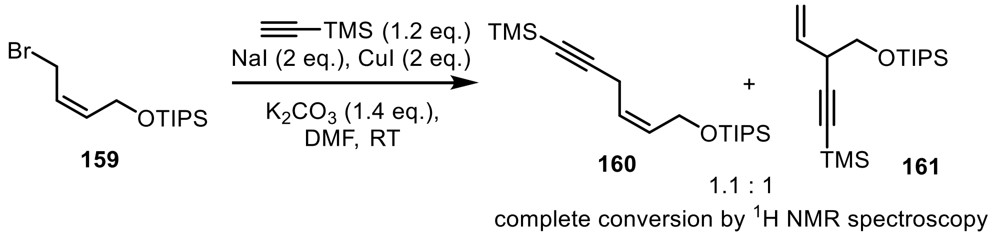
Scheme 32 Side products observed in the attempted synthesis of bromide **153**.

To combat the aforementioned side reactions, alcohol **156** was prepared, protected with a more acid-stable TIPS protecting group. This was done in a similar fashion to the TBS alcohol **143**, adding the TIPSCl dropwise into the reaction mixture over 1 h and affording the mono-alcohol **156** in 66% yield (Scheme 33). This alcohol **156** was then subjected to the Appel conditions as above, and the allylic bromide **159** was isolated cleanly in 84% yield.



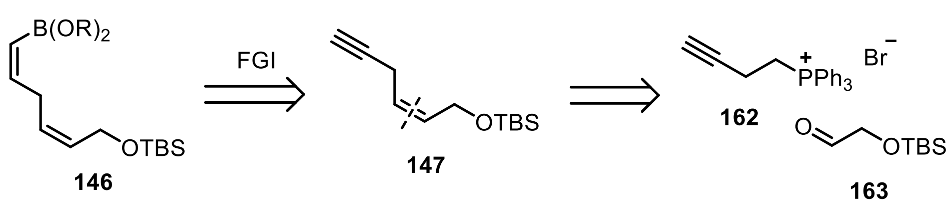
Scheme 33 Further attempts to synthesise **157**.

Unexpectedly, the inclusion of the TIPS protecting group led to poor regioselectivity in the subsequent nucleophilic substitution step, with both the mesylate and bromide leaving groups. A Cu-mediated alkyne coupling with TMS-acetylene was also tested, but this led to almost no regioselectivity (Scheme 34).



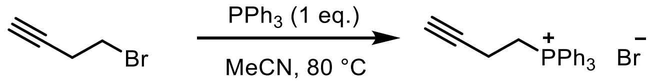
Scheme 34 Cu-mediated coupling attempt.

With changes in the protecting group, leaving group and reaction conditions leading to no significant improvements in selectivity, an alternative approach to alkyne **147** was sought. (*Z*)-Alkenes are commonly formed using a (*Z*)-selective Wittig reaction, and it was thought that this approach might be applied, with the key disconnection across the double bond leading to two known compounds **162**[140] and **163**[141] (Scheme 35).



Scheme 35 Further revised retrosynthetic analysis of vinyl boronate **146**.

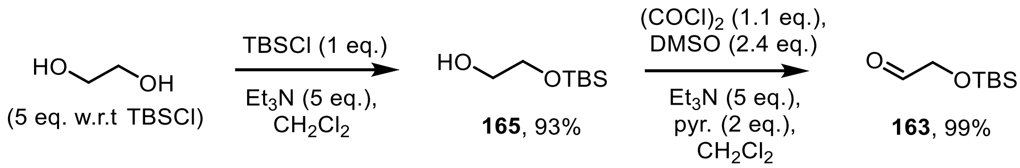
Both the phosphonium bromide salt **162** and aldehyde **163** are readily available in one and two steps respectively from commercially available starting materials. Compound **162** was prepared from 4-bromo-1-butyne **164** by reaction with triphenylphosphine following a literature procedure (Scheme 36).[140]



164 (1.1 eq.) **162**, 94%

Scheme 36 Synthesis of homopropargylic phosphonium salt **162**.

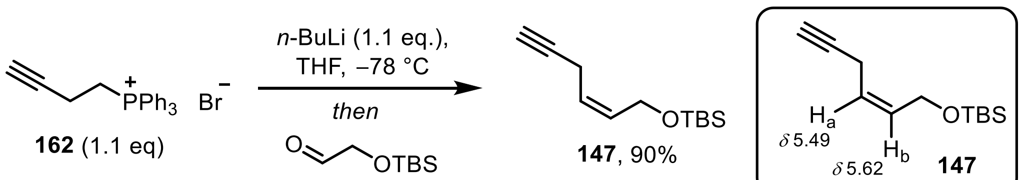
Aldehyde **163** was prepared using literature procedures[141] in two steps: mono-protection of ethane-1,2-diol followed by a Swern oxidation of the resulting alcohol **165** (Scheme 37), with both reactions proceeding in excellent yields.



(5 eq. w.r.t TBSCl) **165**, 93% **163**, 99%

Scheme 37 Synthesis of aldehyde **163**.

With both components in hand, the Wittig reaction was attempted under literature conditions.[140] Pleasingly this proceeded cleanly and stereoselectively to afford the (*Z*)-alkene **147** in excellent yield and as a single isomer, as indicated by the alkene coupling of $^3J_{H\text{–}H}$ = 10.5 Hz (H_a δ 5.49, H_b δ 5.62) in the product (Scheme 38). This sequence of reactions allowed multi-gram quantities of the skipped eneyne **147** to be prepared efficiently.

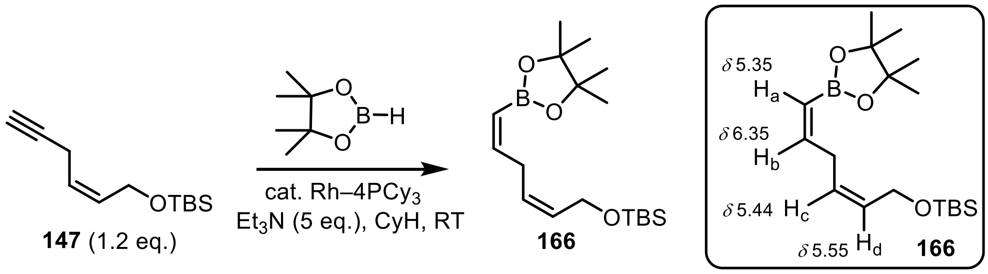


162 (1.1 eq) **163** (1 eq.) **147**, 90%

Scheme 38 Wittig reaction to form skipped eneyne **147**. Inset: ^{1}H NMR chemical shifts (ppm) for selected protons ($CDCl_3$, 400 MHz).

With an efficient route to terminal alkyne **147** now established, the Rh-catalysed *trans*-hydroboration methodology could now be examined. The Rh^I catalyst $[Rh(cod)Cl]_2$ was readily available in one step from $RhCl_3$ using a literature method.[142] Initial attempts at the hydroboration reaction afforded only low yields of the desired product (**166**), but by increasing the catalyst loading and reaction time, synthetically useful yields of the product could be obtained (Table 2). The purity of the starting substrate was also found to be very important; traces of triphenylphosphine from previous steps were found to hinder the reaction and lower the yield. The (*Z*)-stereochemistry of the new double bond was confirmed by the alkene coupling of $^{3}J_{H\text{–}H}$ = 13.7 Hz (H_a δ 5.35, H_b δ 6.36) across the newly formed double bond, which, although large for a (*Z*)-alkene, is a comparable value to that found in similar systems.[135]

Table 2 Optimisation of the Rh-catalysed *trans*-hydroboration reaction.



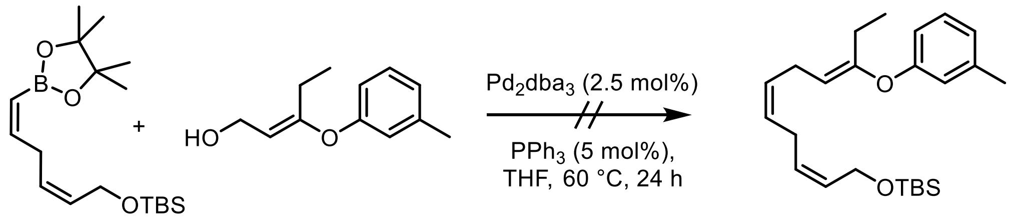
Entry	Catalyst	Loading / mol%	Time / h	Yield / %[a]
1	$[Rh(cod)Cl]_2$	1.5	2	trace[b]
2	$[Rh(cod)Cl]_2$	1.5	17	9%
3	$[Rh(cod)Cl]_2$	3.0	17	27%
4	$[Rh(C_2H_4)_2Cl]_2$	3.0	17	7%
5	$[Rh(cod)Cl]_2$	3.0	44	40%
6	$[Rh(cod)Cl]_2$	6.0	47	47%
7	$[Rh(cod)Cl]_2$	6.0	72	46%

[a]Yield of isolated product **166** following purification on silica gel. [b]Conversion as judged by ^{1}H NMR spectroscopy.

2.2.3 Suzuki–Miyaura Couplings

A search of the literature revealed that there are a number of possible methods under which to effect a Pd-catalysed π-allylic Suzuki coupling. Similar reactions have been performed using allylic alcohols,[143-144] bromides[145-146] and acetates,[147-152] coupling with aryl- and vinyl-boronic acids and esters, and trifluoroborate salts. It was decided to test a range of conditions in order to find the most direct and high-yielding route. Since the allylic bromide appeared to be unstable or inaccessible (Scheme 24, page 52), the coupling reactions were attempted using alcohol **136** and its acetate derivative **137**.

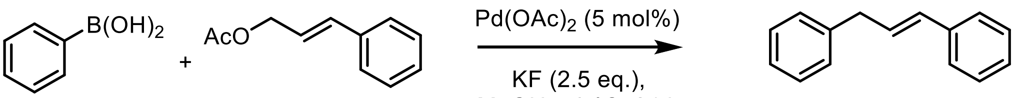
Coupling attempts using the most direct combination of the allylic alcohol and the boronic ester led to no reaction (Scheme 39); the addition of Na_2CO_3 as a base to assist the reaction led to decomposition.



166 **136** **167**

Scheme 39 Coupling attempt of vinyl boronate **166** with allylic alcohol **136**.

A standard set of conditions were next tested on a simple coupling between phenylboronic acid (**168**) and cinnamyl acetate (**169**), resulting in smooth formation of the product (**170**) (Scheme 40).

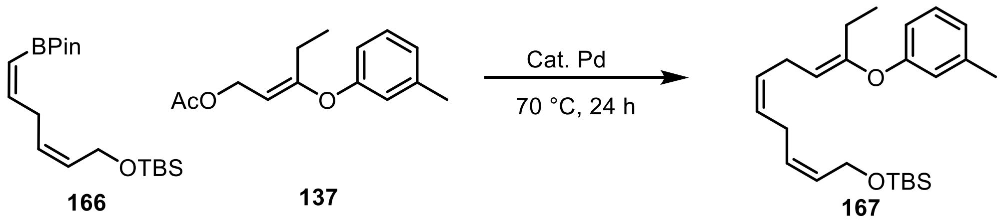


168 **169** **170**, 71%

Scheme 40 Coupling of phenylboronic acid (**168**) with cinnamyl acetate (**169**).

Attempts to apply these same conditions to our system were unsuccessful (Table 3). A variety of conditions were screened, but protic solvents such as methanol appeared to cause rapid decomposition of both substrates (entry 1, Table 3), and in most cases no reaction was observed when THF was employed (entries 2–4, Table 3). Two attempts in which phenylboronic acid was used in place of **166** also failed (entries 5 and 6, Table 3).

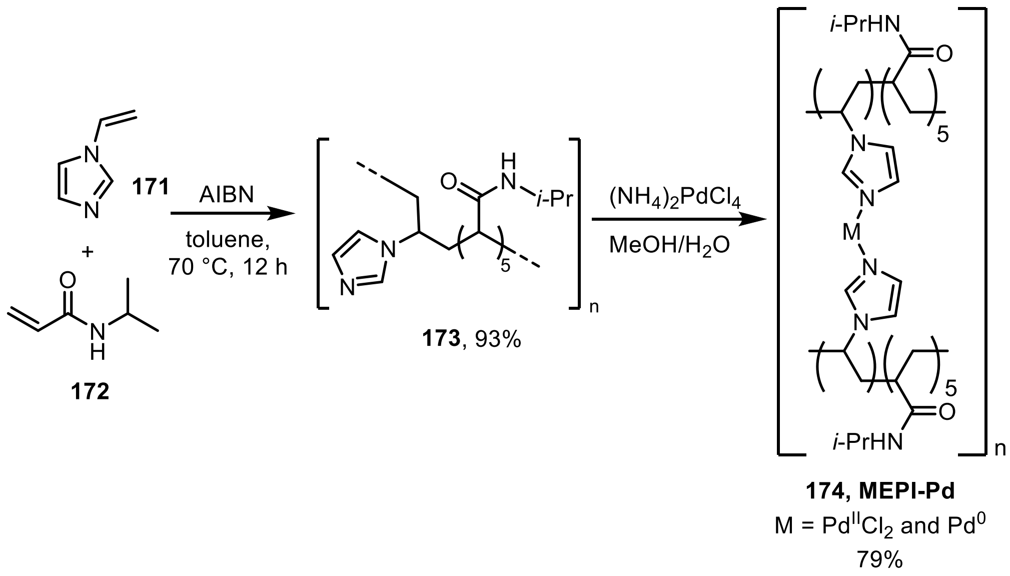
Table 3 Coupling attempts with allylic acetate **137**.



Entry	Boronate	Reagents	Reaction outcome[a]
1	**166**	$Pd(OAc)_2$ (5 mol%), KF, MeOH	decomposition
2	**166**	$Pd(OAc)_2$ (5 mol%), KF, THF	no reaction
3	**166**	$PdCl_2$ (1 mol%), KF, $P(2\text{-}Fu)_3$, THF	SM, some dec.
4	**166**	$PdCl_2$ (1 mol%), KF, $P(2\text{-}Fu)_3$, THF/H_2O	no reaction
5	$PhB(OH)_2$	$PdCl_2$ (1 mol%), KF, $P(2\text{-}Fu)_3$, THF	no reaction
6	$PhB(OH)_2$	$PdCl_2$ (1 mol%), KF, $P(2\text{-}Fu)_3$, MeOH	decomposition

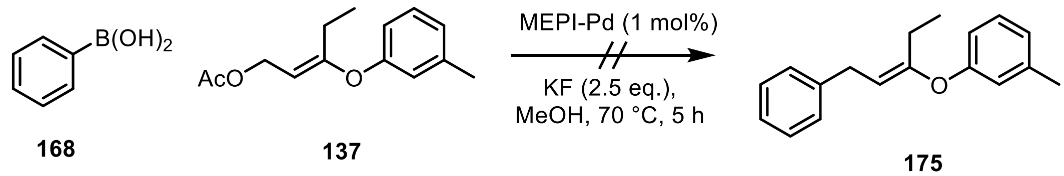
[a]As determined by ^{1}H NMR spectroscopy.

Since conventional catalysis had failed to deliver the desired product, a heterogeneous polymer-supported catalyst, MEPI-Pd **174**, which has been reported to be effective in analogous couplings, was examined next.[149-150] The catalyst is synthesised in two steps: formation of the polymer **173** followed by complexation to Pd (Scheme 41). The Pd is thought to exist in both the Pd^{II} and Pd^0 oxidation states, coordinated by the imidazole moieties on the polymer chain. IR and NMR spectroscopic data of the product **174** were in accordance with the literature.



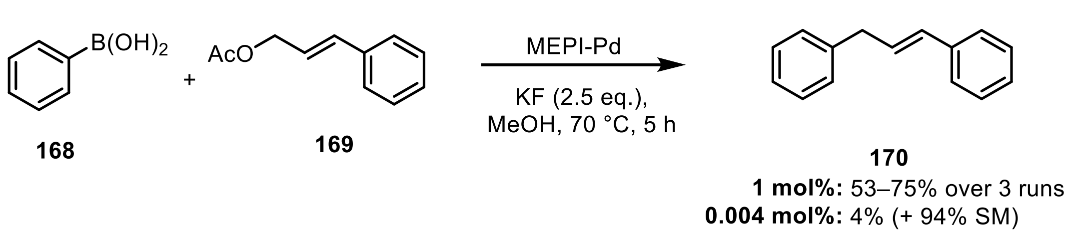
Scheme 41 Synthesis of MEPI-Pd (**174**).

Despite being reported to catalyse allylic Suzuki–Miyaura reactions on a wide variety of substrates, including unactivated aryl chlorides, attempts to apply this catalyst to the coupling of **168** and **137** failed to afford any product, leading to complete decomposition of the allylic acetate (Scheme 42).



Scheme 42 Suzuki reaction employing MEPI-Pd.

Employing these conditions for the coupling of **168** with cinnamyl acetate (**169**) did allow the isolation of some product (**170**), but in variable yields over three runs (Scheme 43). Lowering the catalyst loading to the levels reported in the original publication (0.004 mol%) afforded very low yields even after extended reaction times (22 h) with near-quantitative recovery of starting material.



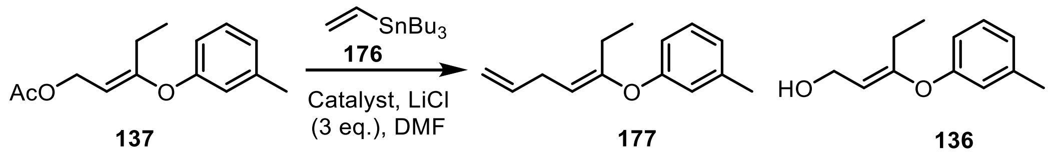
Scheme 43 Test reaction using the MEPI-Pd precatalyst.

2.2.4 Stille Couplings

It was postulated that the reason for the failure of the Suzuki–Miyaura reactions lay with the relatively poor nucleophilicity of the boron reagent. This would make transmetallation onto the π-allyl Pd species slow, resulting in decomposition or no reaction. Thus it was reasoned that if a more reactive organometallic coupling partner, such as an organostannane, was employed, the reaction might be successful. Accordingly, when acetate **137** was stirred with tri-*n*-butyl(vinyl)tin **176** under conditions reported for Stille reactions with allylic acetates,[153] conversion into skipped diene **177** was observed (entry 1, Table 4). Interestingly, it was noted that a small amount of alcohol **136** (*i.e.* deacylated starting material) was also formed in the reaction. Following this encouraging result, an extensive screen of catalysts and conditions was carried out, the key examples of which are shown in Table 4 (for full details see Appendix 2).

Increasing the catalyst loading, equivalents of LiCl and reaction time from the original conditions led to an appreciable increase in product conversion (entry 2, Table 4). Temperature and alternative additives (entries 3 and 4, Table 4) had a detrimental effect on the conversion of the reaction, but use of the catalyst $Pd_2dba_3{\cdot}CHCl_3$ was successful (entry 5, Table 4). The complex $Pd_2dba_3{\cdot}CHCl_3$ can be made by recrystallization of $Pd_2dba_3{\cdot}dba$ from $CHCl_3$ solution is thought to be generally of a higher purity.[154-155] When the catalyst was changed to Pd(*N*-succ)Br$(PPh_3)_2$ (**23**), no reaction took place (entry 6, Table 4) unless the reaction mixture was exposed to trace air (removal of the stopper on the reaction vessel for 5 seconds), in which case all of the starting material was consumed, forming the desired product, and the alcohol side-product in a 4:1 ratio (entry 7, Table 4). If the exposure to air was increased to 20 seconds, the conversion dropped, and this was presumed to be due to increased homocoupling of the organostannane to form volatile butadiene. Attempts with other oxidants such as NMO or $NaBO_3$,[156] or other catalysts such as ABCat[157] (Figure 22) or $PdCl_2(MeCN)_2$ led to little or no conversion to product (entries 9–13, Table 4). The interesting effect of the presence of air on the activity of the catalyst to Pd(*N*-succ)Br$(PPh_3)_2$ has been investigated more thoroughly and is discussed in Chapter 4. Increasing the temperature of the reaction led to increased product formation (and no formation of the previously observed alcohol side product **136**) but also resulted in scrambling of the stereochemistry of the enol ether double bond (entries 14 and 15, Table 4).

Table 4 Optimisation of allylic Stille reaction.



Entry	Catalyst [mol%]	Oxidant [eq.]	Ratio 137:177:136[a]
1	Pd_2dba_3·dba [3]	-	34:58:7
2	Pd_2dba_3·dba [6][b, c]	-	24:62:14
3	Pd_2dba_3·dba [3][d]	-	44:42:14
4	Pd_2dba_3·dba [3][e]	-	83:17:0
5	Pd_2dba_3·$CHCl_3$ [3][c]	-	31:65:4
6	*trans*-**23** [3]	-	89:11:0
7	*trans*-**23** [3]	air [5 s]	0:80:20
8	*trans*-**23** [3]	air [20 s]	13:66:21
9	*trans*-**23** [3]	$NaBO_3$·$4H_2O$ [0.1]	76:24:0
10	*trans*-**23** [3]	NMO [0.2]	90:10:0
11	Pd(dppf)(*N*-succ)Br [3]	-	100:0:0
12	ABCat [1.5]	-	83:17:0
13	$PdCl_2(MeCN)_2$ [3]	-	59:32:8
14	*trans*-**23** [3][f]	-	52:48[g]:0
15	*trans*-**23** [3][h]	-	0:100[i]:0

[a]As determined by ^{1}H NMR spectroscopy. [b]Reaction time 48 h. [c]6 eq. LiCl used. [d]Reaction conducted at 50 °C. [e]TBAC (1 eq.) used in place of LiCl. [f]Reaction carried out at 40 °C. [g]*E*:*Z* = 3:1. [h]Reaction carried out at 60 °C. [i]*E*:*Z* = 2:1.

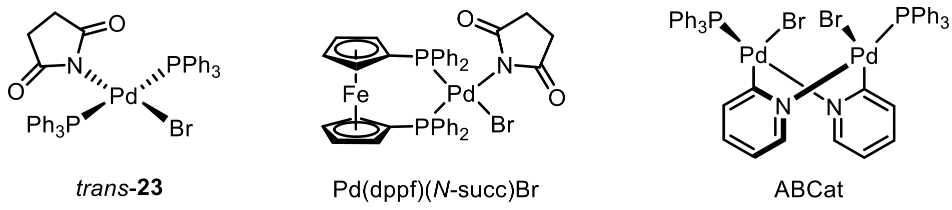
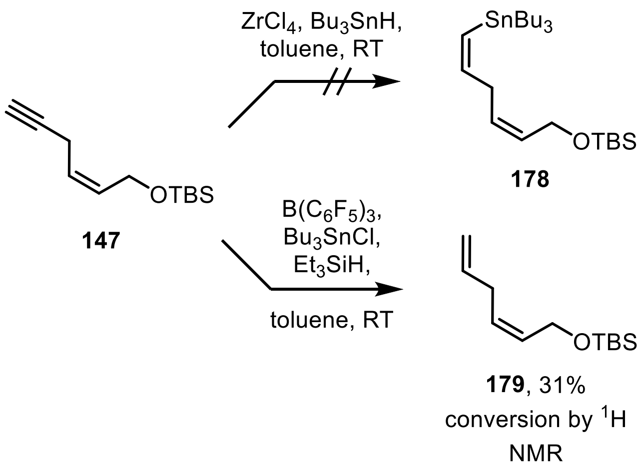


Figure 22 Structures of catalysts in Table 4.

2.2.5 Synthesis of Stannanes

Following these encouraging results, work began towards the synthesis of the tri-*n*-butyltin analogue of the diene coupling partner **178** (Scheme 44). Although (*E*)-vinyl stannanes are readily accessed by radical addition of Bu_3SnH to a terminal alkyne, no general method exists for the synthesis of (*Z*)-vinyl stannanes. Two direct approaches from terminal alkynes have been reported, employing Lewis acids and tin hydrides, and these were explored first.[158-159]

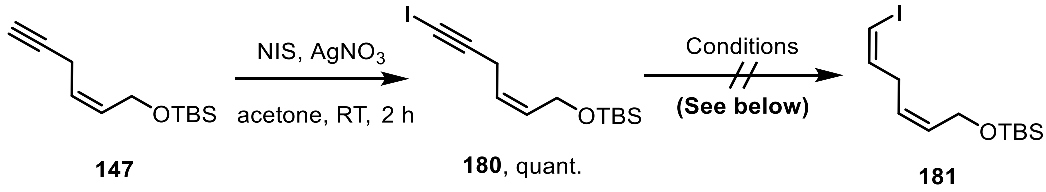
Use of the Lewis acid $ZrCl_4$ resulted in recovery of starting material only; using the more reactive Lewis acid $B(C_6F_5)_3$ along with *in situ* generated Bu_3SnH also failed, giving only modest conversion to the skipped diene product **179** (Scheme 44).



Scheme 44 Direct hydrostannylation attempts on alkyne **147**.

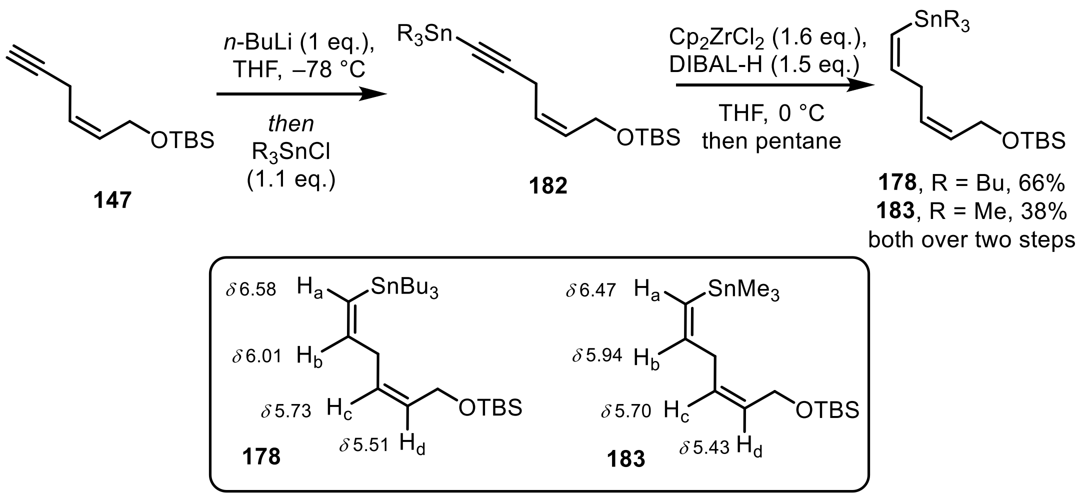
An alternative method for the construction of (*Z*)-vinyl stannanes *via* a vinyl iodide was considered. These compounds can be converted into the desired stannane, either by lithiation (lithium–halogen exchange) and trapping with a tin-based electrophile,[160] or by Pd-catalysed cross-coupling with Sn_2Me_6.[161] (*Z*)-Vinyl iodides are commonly synthesised by diimide reduction of alkynyl iodides with various reagents. The required alkynyl iodide **180** was readily synthesised from the terminal alkyne **147**, but attempts to reduce this with nosylhydrazide[162] or dipotassium azo-1,2-dicarboxylate[163] to form the vinyl iodide **181** failed (Table 5).

Table 5 Attempts towards vinyl iodide **181**.



Entry	Conditions	Reaction outcome
1	$(KO_2CN)_2$ (5 eq.), pyr., AcOH, MeOH	over-reduction
2	$(KO_2CN)_2$ (1.5 eq.), pyr., AcOH, MeOH	complex mixture, some SM
3	*o*-$NO_2C_6H_4SO_2N$=NH, Et_3N, THF/*i*-PrOH	no reaction

A similar but more direct synthetic route would be a (*Z*)-selective reduction of an alkynyl stannane. This transformation can be carried out with Schwartz' reagent, Cp_2ZrClH, a process originally developed by Lipshutz, who applied it to a range of different substrates of varying complexity.[164] Given the difficulties in preparing, handling and storing Schwartz' reagent,[165] and also its high cost, we looked to employ a procedure reported by Negishi and co-workers,[166] which generates the desired reagent *in situ* from the considerably cheaper and more shelf-stable precursors Cp_2ZrCl_2 and DIBAL-H. The alkynylstannane **182** could be easily synthesised from the terminal alkyne **147** (Scheme 45), but it was found that limiting the equivalents of *n*-butyllithium to one, keeping the temperature at −78 °C, and the time for lithiation to 10 min were all crucial factors in limiting side reactions of the skipped eneyne. The highly labile alkynyl stannanes were then subjected to the reduction conditions[164] using *in-situ* generated Schwartz' reagent, which afforded either the butyl or the methyl vinyl stannane in 66% and 38% yield respectively over two steps, both as isomerically pure compounds. The assignment of a (*Z*)-configuration to the newly formed double bonds was supported by the observation of the coupling constants across the alkene of $^3J_{H\text{–}H}$ = 12.3 Hz and 12.2 Hz, and $^3J_{^{119}Sn\text{–}H}$ = 141.6 Hz and 153.2 Hz for **178** and **183** respectively (**178** H_a δ 6.58, H_b δ 6.01; **183** H_a δ 6.47, H_b δ 5.94), which are comparable values to those reported for similar (*Z*)-vinylstannanes.[167] Whilst considerably more labile than the analogous vinyl boronate ester **166**, stannanes **178** and **183** could be purified by flash chromatography by pre-treating the silica gel with 1% triethylamine, and could be stored for several weeks at 3 °C with minimal decomposition.



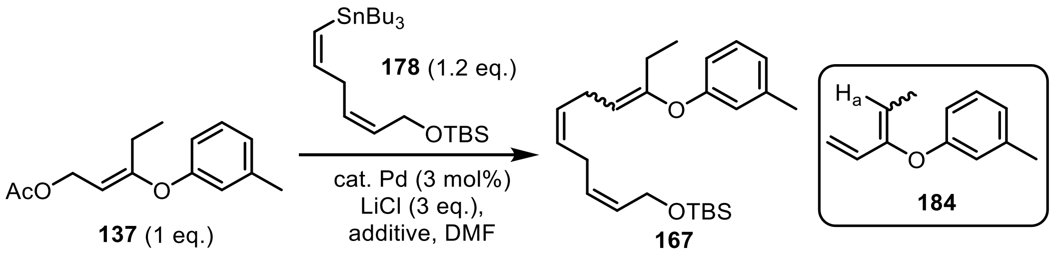
Scheme 45 Synthesis of vinyl stannanes **178** and **183**. Inset: ^{1}H NMR chemical shifts (ppm) for selected protons (C_6D_6, 400 MHz (**178**) or 500 MHz (**183**)).

2.2.6 Coupling of Fragments

With an efficient route to the vinyl stannane established, the Stille coupling under the optimised conditions found earlier could be attempted. Tributylstannane **178** was used in the Stille cross-coupling reaction with the simple acetate **137**, as a model system in order to avoid wasting valuable advanced intermediates (Table 6).

Initial attempts with *trans*-Pd(*N*-succ)Br(PPh_3)$_2$ (*trans*-**23**) in the presence of trace air did not furnish any product, leading only to no reaction and homocoupling of the vinyl stannane (entry 1, Table 6). Increasing the temperature to 90 °C under an inert atmosphere led to partial conversion to product in an *E*/*Z* ratio of 1.5:1 (entry 2, Table 6). The presence of minor side-products in the reaction mixture was also noted, possibly the β-hydride elimination side-product **184** (as suggested by a distinctive quartet in the ^{1}H NMR spectrum, δ 5.24, J = 7.2 Hz, feasibly corresponding to H_a) along with compounds arising from protodestannylation and homocoupling of stannane **178**. Lowering the temperature to 60 °C and extending the reaction time led to no change in the *E*/*Z* ratio, but complete consumption of the starting material and less side-product formation (entry 3, Table 6). The transmetallation step in the catalytic cycle is known to be rate-limiting in many Stille reactions,[168-169] but the use of Cu^I salts[170-171] and weakly coordinating ligands such as $AsPh_3$ or P(2-Fu)$_3$[172] has been shown to speed this up. Indeed the addition of Cu^I salts led to considerable improvements in the *E*/*Z* ratio (entries 4–6, Table 6), with CuCl (entry 6, Table 6) offering the best improvement and also the cleanest reaction. As a comparison, a reaction was run under literature conditions as above (Table 4),[153] resulting in incomplete consumption of starting material and an *E*/*Z* ratio of 1.6:1 as judged by ^{1}H NMR spectroscopy (entry 7, Table 6).

Table 6 Screening of conditions for Stille couplings of **137** and **178**.

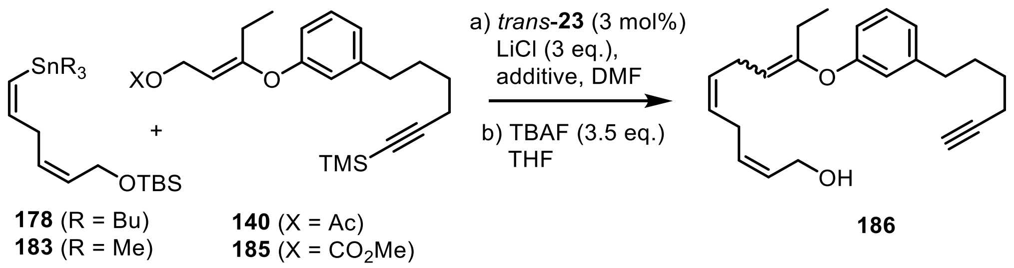


Entry	Catalyst	Additive (eq.)	Time / h	Temp. / °C	Ratio 137:167[a]	*E*:*Z* ratio in 167[a]
1[b]	*trans*-**23**	air (5 s)	24	RT	100:0[c]	-
2	*trans*-**23**	none	3	90	38:62	1.5:1
3	*trans*-**23**	none	24	60	0:100	1.5:1
4	*trans*-**23**	CuI (0.2)	24	60	0:100	2.5:1
5	*trans*-**23**	CuI (1)	18	60	0:100	3:1
6	*trans*-**23**	CuCl (1)	23	60	0:100	3.5:1
7	$Pd_2dba_3{\cdot}CHCl_3$	*i*-Pr_2NEt (1.5)	22	40	40:60	1.6:1

[a]Estimated by ^{1}H NMR spectroscopy of unpurified reaction mixture. [b]Reaction performed in DMF/THF 1:1. [c]As determined by TLC.

With both fragments in hand, the most successful conditions (entry 6, Table 6) were applied to the coupling between allylic acetate **140** and vinyl stannane **178**, with the CuCl additive leading to the isolation of the desired product **186** in 51% yield after silyl deprotection using TBAF (entry 2, Table 7). A further optimisation was briefly carried out, which involved testing the allylic carbonate **185** in the cross coupling, since similar carbonates have been reported to be excellent coupling partners in allylic Stille reactions.[173-174] The required carbonate **185** could be readily accessed in 60% yield using a literature procedure.[175] This substrate proved to be unreactive at RT (entry 3, Table 7), and at higher temperatures led only to decomposition (entry 4, Table 7). Trimethyltin compounds are known to offer increased reactivity over their more commonly used tributyltin analogues, although they are considerably more toxic. It was anticipated that using the trimethyltin analogue **183** might further accelerate the transmetallation step of the reaction, thereby improving the *E*/*Z* selectivity. When this substrate was employed in the Stille reaction, a repeatable *E*/*Z* ratio of 3:1 could be obtained (entry 5, Table 7), and the reaction was appreciably faster. The deprotected alcohol **186** could once again be isolated, after treatment with TBAF and purification on silica gel, in 73% yield over two steps. Removing the CuCl additive (entries 6–7, Table 7) and lowering or raising the reaction temperature (entries 7–8, Table 7) led to a decrease in yield and/or selectivity.

Table 7 Application of Stille reaction to full system and further optimisation.



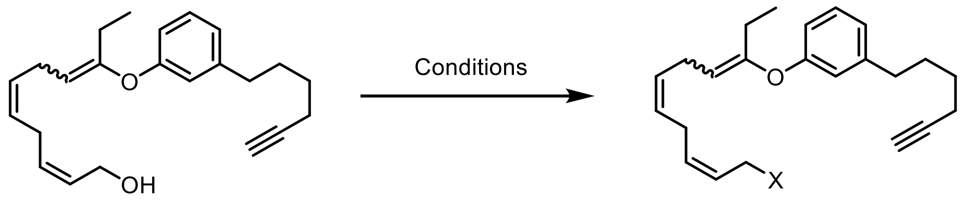
Entry	R	X	Additive	Time / h	Temp / °C	Yield / %[a]	*E*/*Z*[b]
1	Bu	Ac	CuI (1 eq.)	22	60	24	1.7:1
2	Bu	Ac	CuCl (1.2 eq.)	17	60	51	2.3:1
3	Bu	CO_2Me	H_2O (2 eq.)	5	RT	0[c]	-
4	Bu	CO_2Me	none	7	60	dec.[c]	-
5	Me	Ac	CuCl (2 eq.)	4.5	60	73	3:1
6	Me	Ac	none	3	60	36	1.6:1
7	Me	Ac	none	2	40	0[c]	-
8	Me	Ac	CuCl (2 eq.)	2	70	52	3:1

[a]Yield of isolated product over two steps, following purification on silica gel. [b]Estimated by ^1H NMR spectroscopy. [c]As determined by ^1H NMR spectroscopy.

2.2.7 Ring Closure Attempts

A variety of conditions were envisioned to be potentially suitable for the final ring closing reaction. The allylic alcohol group could be activated in a number of different ways, and Cu^I salts are known to mediate reactions between terminal alkynes and allylic electrophiles.[176-178] Similarly, allylic chlorides, bromides and acetates are known to react with zincated terminal alkynes under Pd catalysis.[179] Whilst the use of strong bases such as *n*-BuLi was unlikely to be compatible with this complex substrate, it was hoped that zincation could be achieved under milder conditions using $Zn(OTf)_2$ and Et_3N.[180-181] Initial attempts to form a tosylate or mesylate group from the allylic alcohol under standard conditions led to either return or decomposition of starting material (Table 8, entries 1–4). In contrast to this, acetylation under standard conditions led to a 100% conversion into the desired product (entry 5, Table 8).

Table 8 Attempted functional group transformations of allylic alcohol **186**.



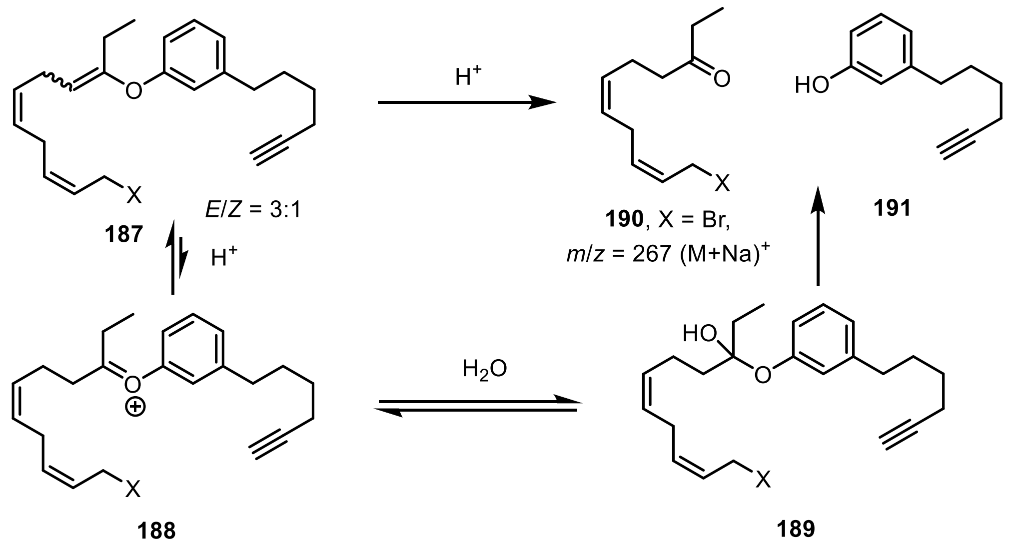
186, *E*/*Z* = 3:1 **187**, *E*/*Z* = 3:1

Entry	**X**	**Conditions**	**Time / h**	**Temp / °C**	**Reaction outcome**[a]
1	OTs	TsCl, Et_3N, CH_2Cl_2	20	RT	Decomposition
2	OTs	TsCl, pyridine	2	RT	No reaction
3	OTs	TsCl, pyridine	17	50	SM/partial dec.
4	OMs	MsCl, Et_3N, THF	2.5	RT	SM/partial dec.
5	OAc	Ac_2O, Et_3N, DMAP, CH_2Cl_2	1.5	RT	100% conversion
6	OMs	Ms_2O, Et_3N, DMAP, CH_2Cl_2	3	RT	Ether cleavage[b]
7	Br	PBr_3, Et_2O	2	0	Ether cleavage[b]
8	OMs	Ms_2O, Et_3N, DMAP, CH_2Cl_2	1.5	0 → RT	Partial conversion
9	Br	CBr_4, PPh_3, CH_2Cl_2	1	RT	Decomposition
10	Cl	CCl_4, PPh_3, CH_2Cl_2	3	0 → RT	Decomposition
11	Cl	NCS, Me_2S, CH_2Cl_2	1	−20	Decomposition

[a]As judged by ^{1}H NMR spectroscopy. [b]See Scheme 46.

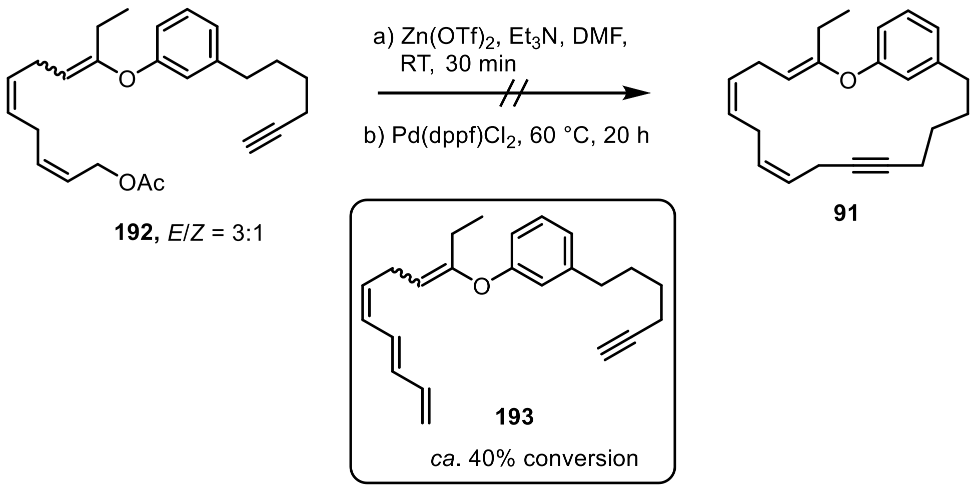
A variety of other conditions were examined, including an attempt to emulate the successful acetylation conditions with methanesulfonic anhydride, and an attempt with PBr_3 (entries 6 and 7 respectively, Table 8) which both led to a clean and complete decomposition *via* cleavage of the ether bond (Scheme 46). However, in the former case, reducing the reaction time and temperature led to the formation of some of the desired product by ^{1}H NMR spectroscopy (entry 8, Table 8), although the precise conversion could not be determined accurately. Further attempts using the Appel (entries 9 and 10, Table 8) and Corey–Kim (entry 11, Table 8) reactions also led to decomposition.

The cleavage of the vinyl ether bond was presumed to be acid mediated. This could potentially occur either under the reaction conditions from trace water, or during workup (Scheme 46). The pseudomolecular ion for ketone **190** (X = Br) was observed by mass spectrometry (ESI), and both structures are consistent with the expected chemical shifts in the crude ^{1}H NMR spectrum of the appropriate reaction mixtures.



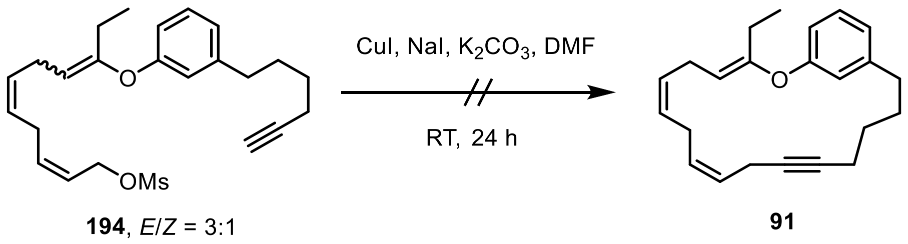
Scheme 46 Potential pathway for enol ether cleavage.

The allylic acetate **192** was subjected to conditions known to effect zincation of terminal alkynes,[180-181] followed by heating with Pd(dppf)Cl_2 (Scheme 47). Unfortunately all attempts at closing the ring in this way afforded only returned starting material, along with the conjugated elimination product **193** (Scheme 47). This result suggests that the zincation step is not effective, and that heating with a base for extended periods leads to elimination of the allylic leaving group from the starting material. An alternative attempt under Sonogashira-type conditions (CuI, Pd(dppf)Cl_2, Cs_2CO_3) led to no product formation.



Scheme 47 Attempted ring closure of allylic acetate **192**.

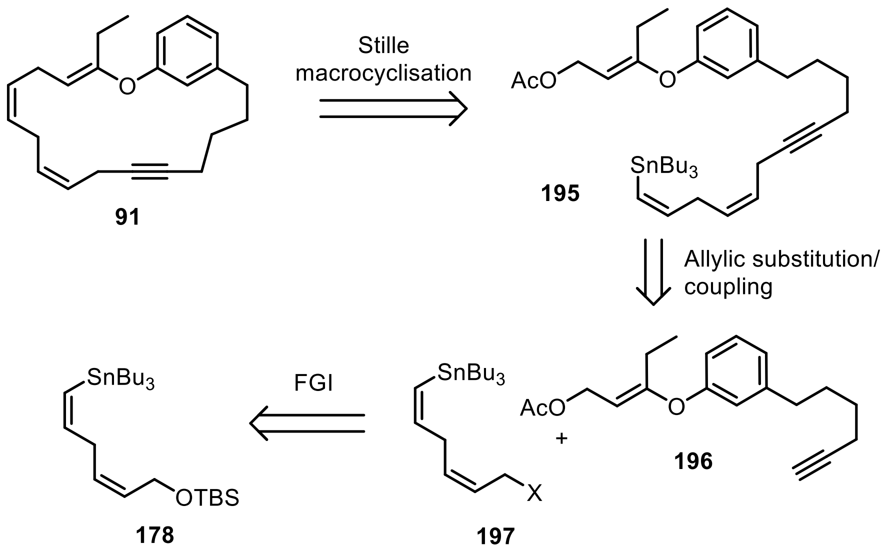
Similarly, the allylic mesylate **194** which was the crude product of the mesylation reaction (entry 8, Table 8) was subjected to a Cu^I-mediated substitution reaction, but this afforded only decomposition and no product could be discerned by ^{1}H NMR spectroscopy or ESI-MS (Scheme 48).



Scheme 48 Attempted ring closing with mesylate **194**.

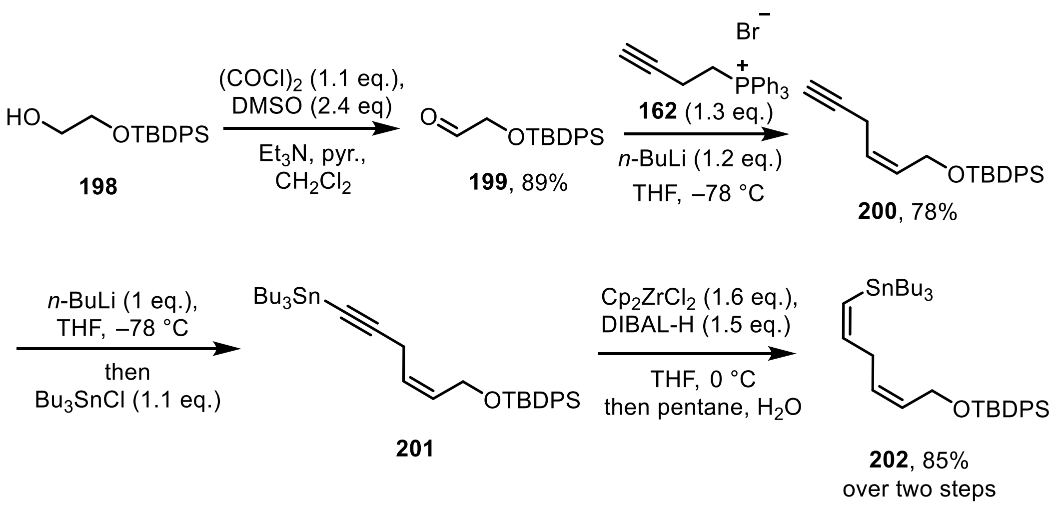
2.2.8 Reversal of key steps

One possible contingency plan involved reversing the key steps in the synthesis, *i.e.* carrying out the allylic substitution reaction prior to a Stille cross-coupling macrocyclisation reaction (Scheme 49). This would have the advantage of avoiding any problematic functional group interconversions, not forming the sensitive triply skipped alkene system until the final step. The silyl-protected allylic alcohol **178** would make an ideal precursor to the corresponding allylic bromide or chloride. Then using either a Cu-mediated substitution reaction or Pd-catalysed coupling of an alkynyl zinc reagent, it was anticipated that good chemo- and regioselectivity could be obtained, in addition to stereospecificity.



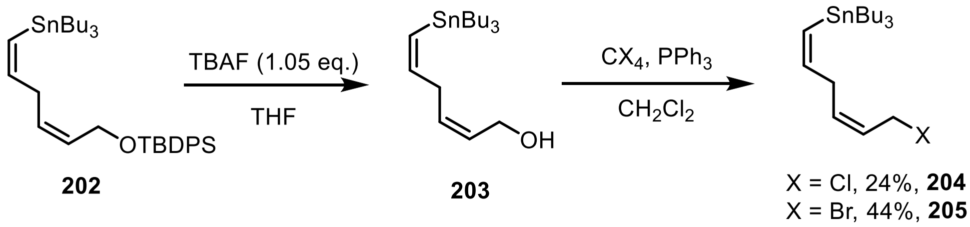
Scheme 49 Revised retrosynthetic analysis of compound **91**.

Due to previously encountered volatility problems during the synthetic sequence leading to stannane **178**, at this stage the TBS protecting group was swapped for a bulkier TBDPS group. This enabled the synthesis of the key intermediate **200** to be carried out more reliably, and also improved the yield of the stannylation–reduction step, affording the (*Z*)-vinyl stannane **202** in 85% yield (Scheme 50).



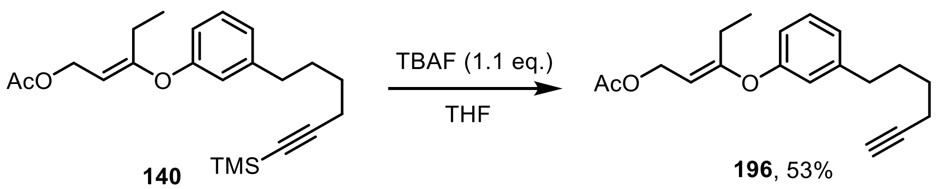
Scheme 50 Synthesis of vinyl stannane **202** with a TBDPS protecting group.

The new protecting group was then smoothly removed using TBAF, and the resulting allylic alcohol (**203**) converted into the corresponding chloride (**204**) or bromide (**205**) under Appel conditions (Scheme 51). In both cases the Appel reactions were unexpectedly sluggish, affording only partial conversion and recovery of starting material.



Scheme 51 Conversion of stannane **202** into allylic halides **204** and **205**.

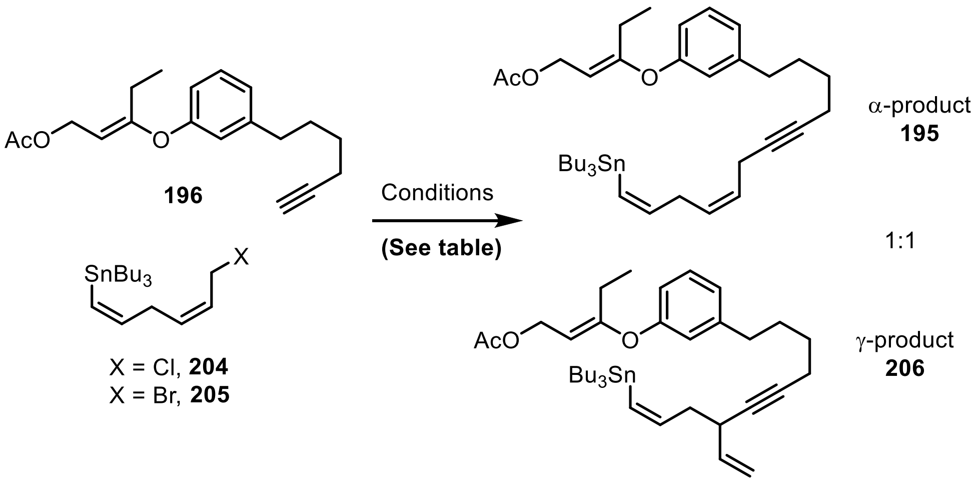
The silyl protected terminal alkyne **196** was also deprotected using TBAF (Scheme 52). The terminal alkyne **196** could also be synthesised directly from the ester **139** in 71% over three steps.



Scheme 52 Deprotection of silyl-protected alkyne **140**.

With these two key fragments in hand, conditions for the substitution reaction were screened (Table 9). An attempt to use the Negishi conditions[179] to form a zincated alkyne using *n*-BuLi led only to decomposition of the substrate (entry 1, Table 9). When Cu^{I} salts were employed to mediate the reaction, partial conversion to the desired product **195** was observed (entries 2–5, Table 9); disappointingly, the product was formed in a 1:1 mixture along with the unwanted γ-isomer (**206**), resulting from S_N2' substitution, and these proved inseparable by chromatography. Superior conversions were obtained when stoichiometric Cu was used along with NaI with the allylic chloride (entry 5, Table 9). This allowed isolation of the products in 40% isolated yield after column chromatography.

Table 9 Screening of reaction conditions for alkyne substitution reaction.



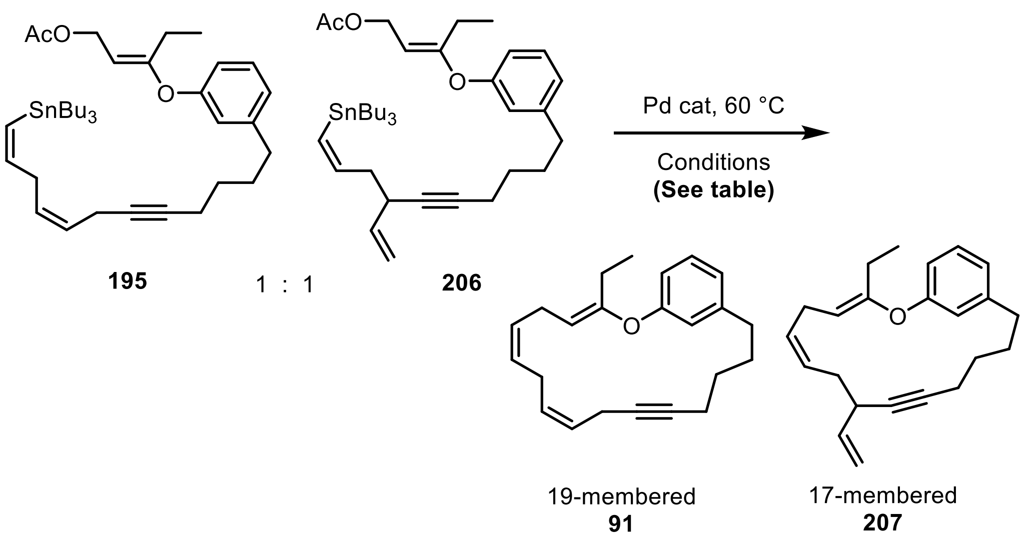
Entry	X	Conditions	Time / h	Temp / °C	Reaction outcome[a]
1	Br	*n*-BuLi, ZnBr, Pd(dppf)Cl_2	14	RT	decomposition
2	Br	CuI, TBAC, K_2CO_3, DMF	21	RT	38% conv.
3	Br	CuI, NaI, K_2CO_3, DMF	24	RT	34% conv. (11% isol.[b])
4	Cl	CuI, TBAC, K_2CO_3, DMF	22	RT→50	17% conv. (5% isol.[b])
5	Cl	CuI, NaI, K_2CO_3, DMF	20	RT	40% isolated[b]

[a]As judged by ^{1}H NMR spectroscopy. [b]Combined yield of product mixture following column chromatography.

2.2.9 Stille Macrocyclisations

Despite the inseparability of the mixture of regioisomers, it was considered instructive to test the macrocyclisation reaction on this mixture of compounds as a proof of principle, before finding a more efficient route to the required Stille precursor (**195**) as a single compound. The mixture of isomers (**195** and **206**) was therefore subjected to the Stille conditions used previously (see Table 7) at a range of substrate concentrations. At lower concentrations (1–5 mM) the reactions all resulted in loss of the tributyltin group, either using *trans*-**23** (entries 1–3, Table 10) or the Farina conditions[172] of $Pd_2dba_3 \cdot CHCl_3$ and $AsPh_3$ (entries 4–5, Table 10), conditions often employed in Stille macrocyclisations.[32] Presumably this protodestannylation was caused by adventitious acid in the DMF solvent, although it was still observed even in the presence of DIPEA base. Increasing the concentration to 20 mM led to no reaction with *trans*-**23** (entry 6, Table 10), but using the Farina conditions full consumption of starting material was observed along with the formation of a new mixture of compounds, suspected to be the cyclisation products **91** and **207**. Repetition of the reaction on a larger scale and for a shorter reaction time allowed isolation of the products as a mixture in *ca*. 60% yield, and positive confirmation of their identity by ^{1}H NMR and APCI-MS (observed 321.2210 $[M+H]^{+}$, required 321.2213). It was not possible to assign the structures of minor isomers (*e.g. E*/*Z* isomers around the enol ether double bond) due to the small scale of the reaction, but analysis of the ^{1}H NMR spectra with the aid of COSY experiments strongly suggested the formation of both the expected macrocycles **91** and **207**. An attempt to separate any isomers using $AgNO_3$-impregnated preparative TLC led to loss of the product mixture.

Table 10 Screening of conditions for Stille macrocyclisation.



Entry	Conditions	[SM] / mM	Time / h	Reaction outcome[a]
1	*trans*-**23**, LiCl, DMF	1	29	protodestannylation
2	*trans*-**23**, LiCl, DMF	5	28	protodestannylation/ β-hydride elimination
3	*trans*-**23**, CuCl, LiCl, DMF	5	19	protodestannylation
4	$Pd_2dba_3 \cdot CHCl_3$, $AsPh_3$, LiCl, DIPEA, DMF	5	5	protodestannylation
5[b]	$Pd_2dba_3 \cdot CHCl_3$, $AsPh_3$, LiCl, DIPEA, CyH	5	72	protodestannylation
6	*trans*-**23**, LiCl, DMF	20	29	unreacted SM
7	$Pd_2dba_3 \cdot CHCl_3$, $AsPh_3$, LiCl, DIPEA, DMF	20	2.5	full conversion
8	$Pd_2dba_3 \cdot CHCl_3$, $AsPh_3$, LiCl, DIPEA, DMF	20	1.5	*ca*. 60% isol. Yield[c]

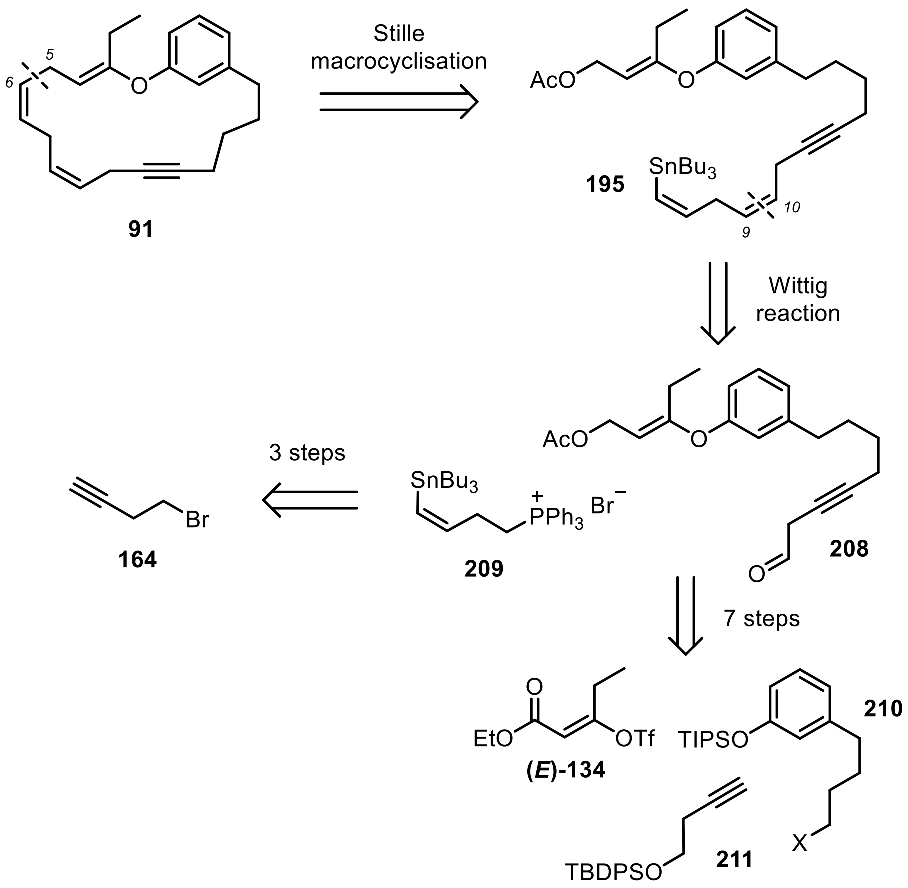
[a]As judged by ^{1}H NMR spectroscopy. [b]Temperature increased to 80 °C. [c]Combined yield of product mixture following column chromatography.

This positive result served as a proof of principle that this was a viable strategy for the formation of the macrocyclic ring. The only challenge remaining was to find an efficient and reliable route to compound **195** as a single isomer.

2.3 Second Generation Approach

2.3.1 Revised Retrosynthetic Analysis

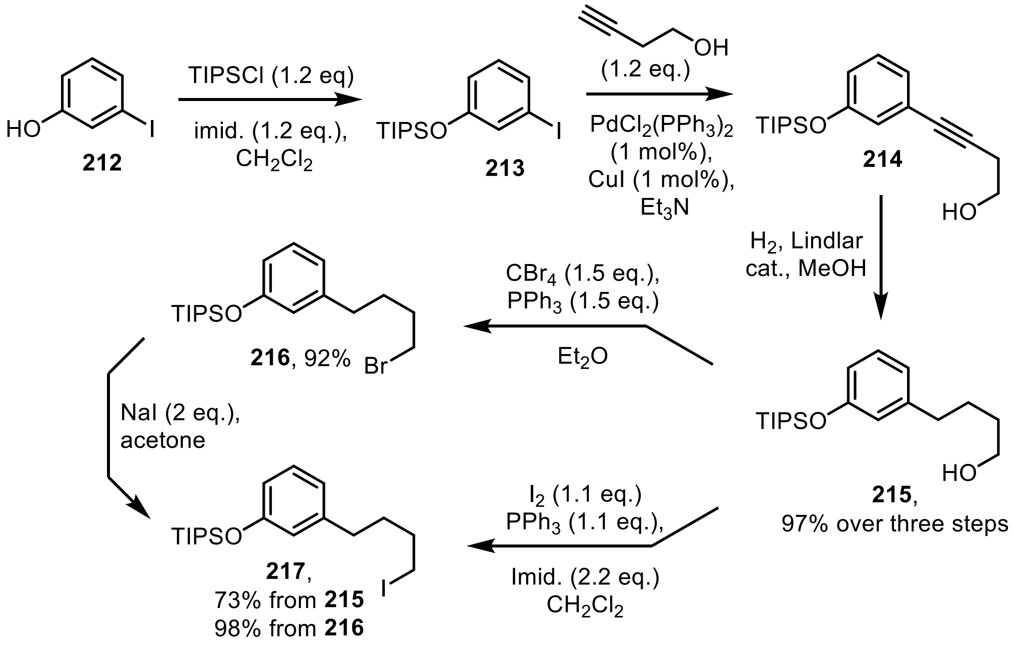
An alternative route to the Stille precursor was thus proposed, which would allow its isolation as a single stereo- and regioisomer. This revised strategy involved using a late-stage Wittig reaction between C-9 and C-10 to introduce the vinyl stannane group in a stereoselective manner (Scheme 53), giving rise to eastern (**208**) and western (**209**) precursor fragments. The aldehyde **208** would be available using the chemistry already developed from three known building blocks ((*E*)**-134**, **210** and **211**). The phosphonium salt **209** was anticipated to be accessible from bromobutyne (**164**) in three steps.



Scheme 53 Second generation revised retrosynthetic analysis.

2.3.2 Construction of the Eastern Fragment

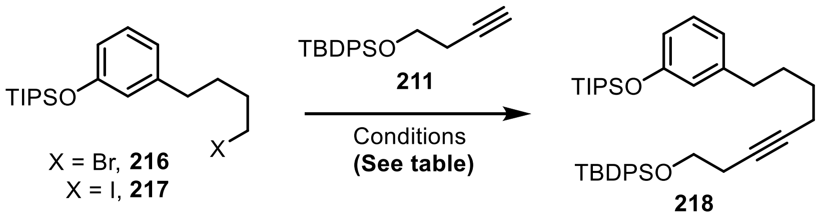
In considering the retrosynthesis of the required alkylated phenol, a scaleable and efficient route was sought to allow as much material as possible to be brought through the early reactions. The route began with silyl protection of 3-iodophenol **212** with a TIPS group, chosen to be orthogonal to the TBDPS group which would be introduced later in the synthesis. The carbon–carbon bond was then formed using an efficient Sonogashira reaction on the aryl iodide; the resultant triple bond in **214** could be reduced giving **215** and the hydroxyl moiety readily converted to a bromide (**216**) or iodide (**217**) leaving group (Scheme 54).[182]



Scheme 54 Synthesis of alkyl bromide **216** and alkyl iodide **217**.

Alkylations of terminal alkynes with alkyl halides have been reported in the literature under a variety of conditions.[183-185] A screening of conditions was carried out, selected examples of which are shown in Table 11 (for full details, see Appendix 2). No significant formation of product (**218**) could be observed when using the bromide **216** as the electrophile (entries 1 and 2, Table 11). Switching to the iodide (**217**) initially gave no improvement (entry 3, Table 11), until an excess of HMPA was employed (entry 4, Table 11), although further increases in the amount led to a decrease in yield (entry 5, Table 11). Several attempts, under conditions reported for alkyl Sonogashira reactions by Fu and co-workers,[186] led to only modest yields being recorded (entries 6 and 7, Table 11).

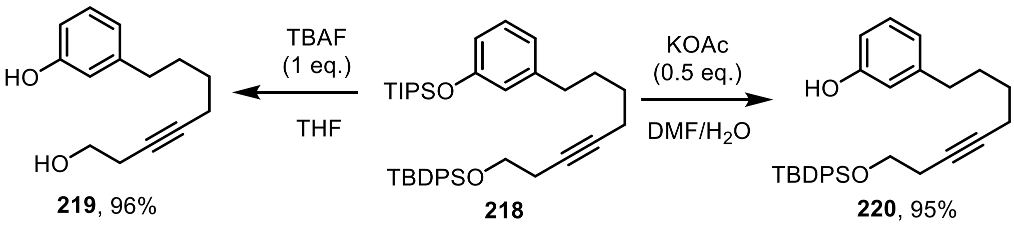
Table 11 Screening of alkylation conditions.



Entry	**X**	**Conditions**	**Temp. / °C**	**Yield / %**[a]
1	Br	*n*-BuLi (1.1 eq.), THF	−78 → 50	no reaction[b]
2	Br	*n*-BuLi (1.5 eq.), HMPA (1 eq.), THF	−78 → 50	trace[b]
3	I	*n*-BuLi (1.2 eq.), HMPA (1.1 eq.), THF	−78 → RT	trace[b]
4	I	*n*-BuLi (1.2 eq.), HMPA (2.4 eq.), THF	−78 → 67	20
5	I	*n*-BuLi (1.2 eq.), HMPA (5 eq.), THF	−78 → 67	7
6	I	$[Pd(allyl)Cl]_2$, IPr·HCl, (4-MeO)-dba, CuI, Cs_2CO_3, DMF/Et_2O	40	13
7	I	$Pd_2(4\text{-MeO-dba})_3$, IPr·HCl, CuI, Cs_2CO_3, DMF/Et_2O	40	7

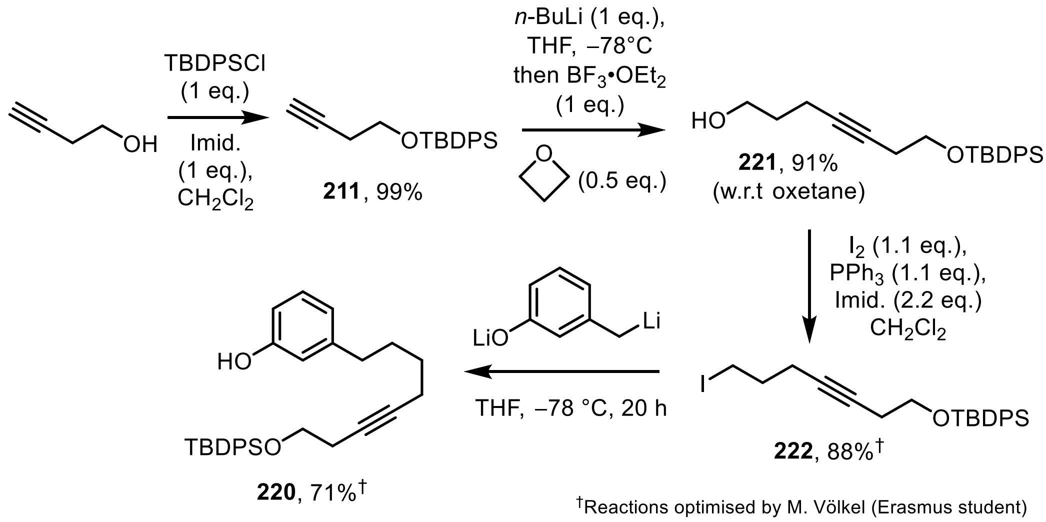
[a]Yield of isolated product following column chromatography. [b]As judged by ^{1}H NMR spectroscopy.

Although attempts to cleave the TIPS group of the bis-silyl ether selectively using only one equivalent of TBAF led to clean formation of the diol **219** (Scheme 55), this transformation could be effected by employing conditions developed by Sun and co-workers which use KOAc in a mixture of DMF and water.[187] However, the low yields obtained in the alkylation reactions (Table 11) made this approach to the target phenol **220** unfeasible.



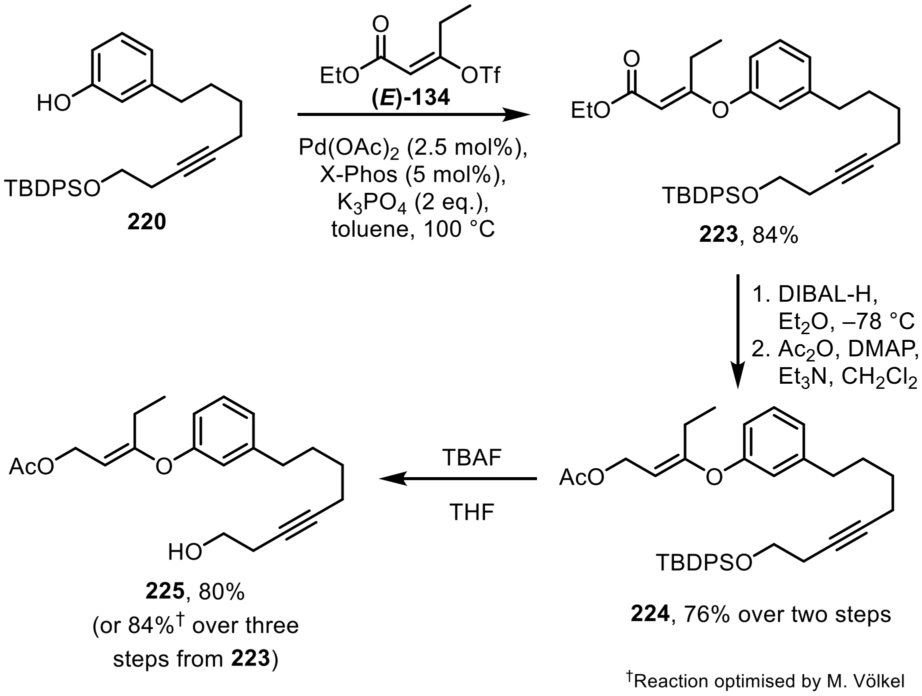
Scheme 55 Attempted (left) and selective (right) deprotection of compound **218**.

The failure of the strategy above led to the exploration of an alternative route to the phenol, mirroring the successful synthesis of phenol **101** used previously. The known terminal alkyne (**211**) was alkylated using oxetane to generate alcohol **221** in high yield (Scheme 56).[188-189] This was then iodinated in a similar fashion to previously, giving iodide **222** in excellent yield. This iodide can be used as the alkylating agent in the *m*-cresol dimetallation reaction utilised earlier. Initial attempts at this reaction gave only low yields of impure products, but it was found that by maintaining a reaction temperature lower than −70 °C for a prolonged period (*ca.* 20 h), side reactions were minimised and the product could be isolated in 71% yield (Scheme 56).



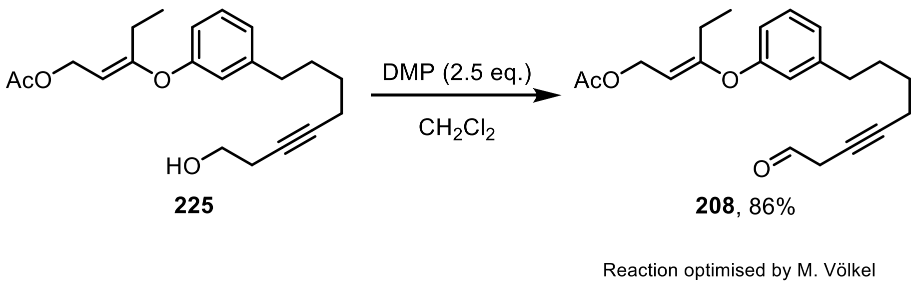
Scheme 56 Synthesis of phenol **220**.

The new alkylated phenol **220** could then be applied in the optimised Buchwald–Hartwig etherification reaction with enol triflate (*E*)-**134**, affording the aryl vinyl ether **223** in good yield (Scheme 57). The ester could then be reduced and acetylated in 76% yield, followed by desilylation using TBAF, providing homopropargylic alcohol **225** in 80% yield. This three-step sequence could also be carried out without purification of the intermediate acetate **224**, allowing isolation of the desired alcohol in 84% yield over three steps (Scheme 57).



Scheme 57 Synthesis of allylic acetate **225**.

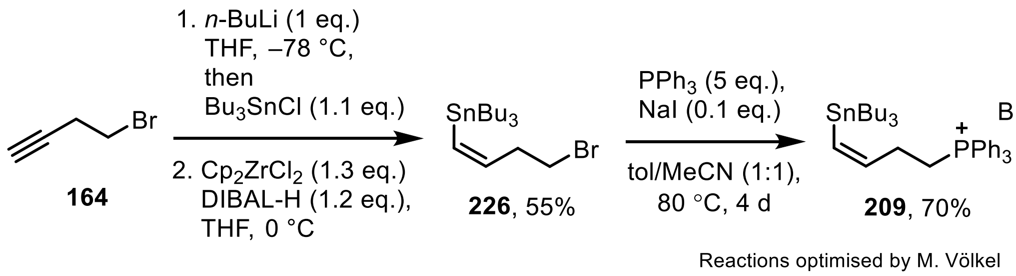
Homopropargylic aldehydes are known to be extremely sensitive compounds, susceptible to isomerisation, primarily due to the high acidity of the propargylic position. However, oxidation reactions of homopropargylic alcohols have been reported using Dess–Martin periodinane,[190] and in this case smooth conversion could be achieved under carefully base- and water-free conditions (Scheme 58). Any attempts to buffer the reaction with $NaHCO_3$, or switch to the Swern oxidation, led to extensive decomposition and side reactions.



Scheme 58 Oxidation of alcohol **225** to form aldehyde **208**.

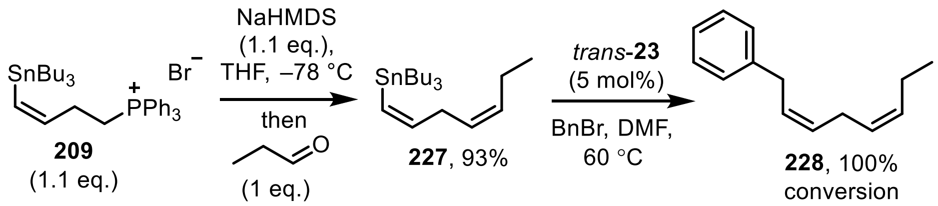
2.3.3 Construction of the Western Fragment

Whilst bifunctional stannane–phosphonium reagents similar to **209** have been briefly described in the literature,[191] their potential for use in the synthesis of skipped dienes has been largely overlooked. We found that the required novel fragment could be readily accessed in three steps from commercially available bromobutyne (**164**) (Scheme 59). Using a similar protocol to that used in the synthesis of **178**, this starting material was lithiated with *n*-BuLi and reacted with tributyltin chloride to afford an alkynylstannane. The use of one equivalent of the organolithium reagent, and a low temperature for the lithiation step (−78 °C) were found to be critical in favouring lithiation of the alkyne over elimination of HBr from either the starting material or the product to form a conjugated eneyne. The crude alkynylstannane was reduced directly using *in situ* generated Schwartz' reagent. Reaction of the resultant bromide (**226**) with triphenylphosphine in a mixture of acetonitrile and toluene with the addition of a catalytic amount of NaI afforded the desired compound **209** as a stable white solid in 70% yield.



Scheme 59 Synthesis of phosphonium reagent **209**.

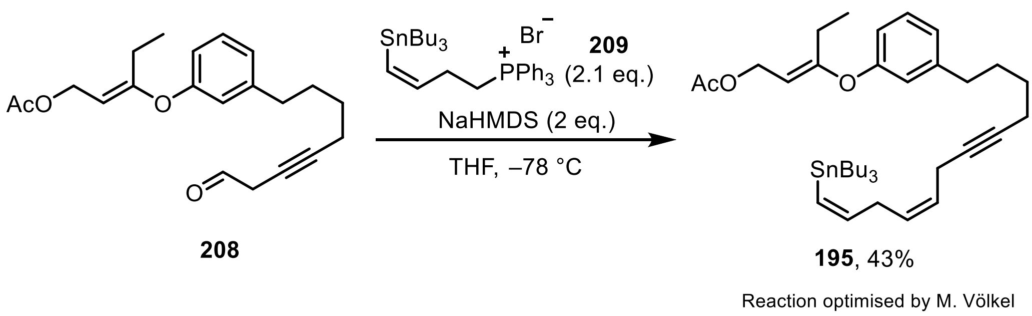
As a test of the feasibility of this fragment as a building block in the construction of skipped dienes, compound **209** was treated with NaHMDS at −78 °C which resulted in an orange solution, suggesting successful formation of a phosphorus ylid. Accordingly, the addition of propionaldehyde led to the smooth formation of the isomerically pure (*Z*,*Z*)-diene **227** which could be isolated in 93% yield, effectively demonstrating the potential of this strategy (Scheme 60). Alkene couplings of $^{3}J_{H–H}$ = 12.3 and 10.7 Hz observed in the ^{1}H NMR spectrum of **227** confirmed the (*Z*,*Z*)-stereochemistry. Subsequent coupling with benzyl bromide using *trans*-**23** resulted in full conversion into the expected product **228** (Scheme 60). Unfortunately due to the volatility of this compound, an accurate yield of the isolated product could not be obtained.



Scheme 60 Demonstration of Wittig–Stille coupling approach to skipped alkenes such as **228**.

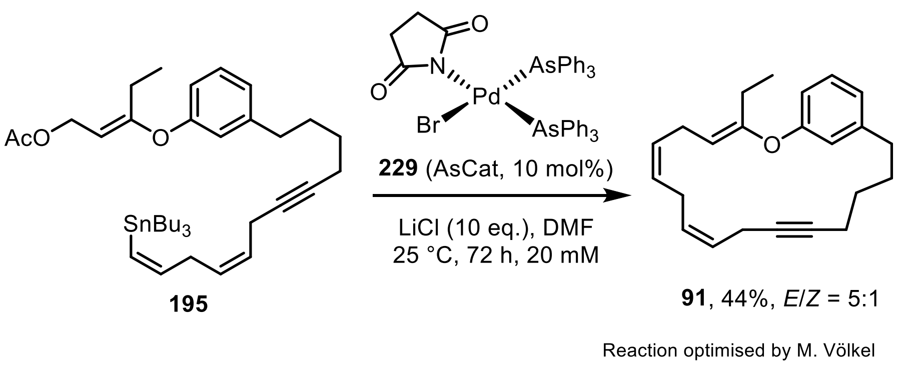
2.3.4 Coupling of Fragments and Ring Closure

With both the eastern and western fragments now in hand, the key Wittig coupling to unite the two fragments was attempted. It was found that the desired stannane (*Z*)-alkene **195** could be obtained in a moderate 43% yield, but with essentially complete stereoselectivity. No side products were isolated or characterised in this reaction, and the low yield obtained was attributed to decomposition of the sensitive aldehyde fragment. The stereochemistry of the new double bond was confirmed by the presence of a $^{3}J_{H\text{–}H}$ = 10.2 Hz coupling in the product.



Scheme 61 Wittig coupling between phosphonium **209** and aldehyde **208**.

The final ring-closing reaction was then attempted, first under the conditions used previously (Table 10), which afforded the product **91** in 28% yield. Encouraged by this, a further attempt using the newly developed catalyst AsCat (**229**, see Chapter 5 for full details) was then undertaken. The reaction was performed under dilute conditions (20 mM), and maintained at 25 °C in order to minimise the isomerisation observed upon heating in previous attempts. Analysis by TLC showed complete consumption of the starting material after 72 h; work up and purification by preparative TLC allowed isolation of the desired macrocycle **91** in 44% yield (Scheme 62).



Scheme 62 Stille macrocyclisation of compound **195** using AsCat **229** to give the target compound **91**.

2.4 Product Characterisation

Compound **91** was isolated in an approximately 5:1 *E*/*Z*-ratio around the enol ether double bond. The expected connectivity and stereochemistry of the final target compound has been found to be in full agreement with ^{1}H NMR, COSY, HSQC, HMBC and NOESY experiments (see Appendix 4 for a full list of correlations). In particular, the nOe correlation between H-5 and H-1′, along with the lack of interaction between H-4 and H-1′, strongly suggest that the expected (*E*)-isomer is the major product (Figure 23).

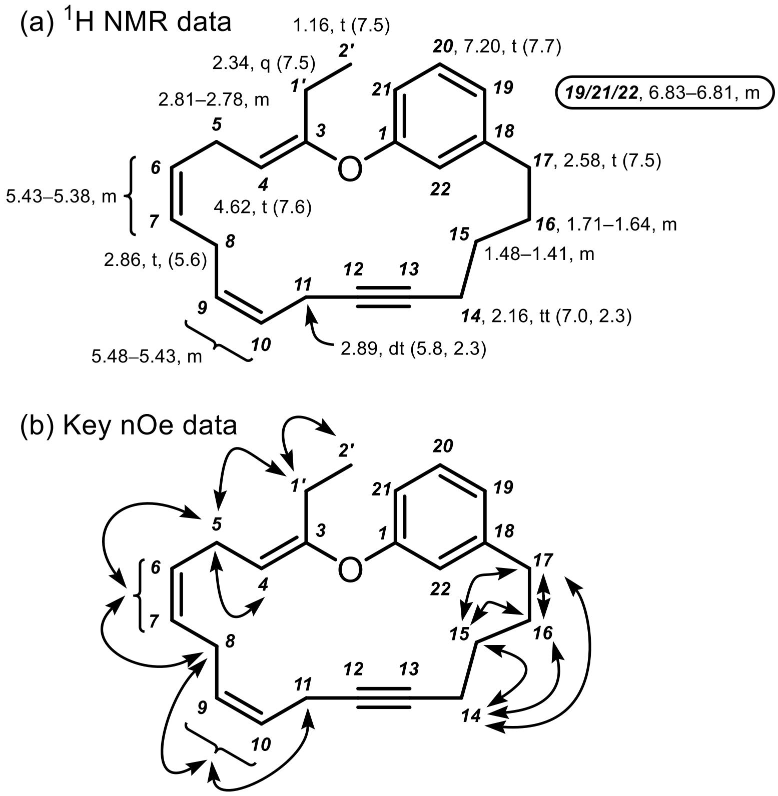
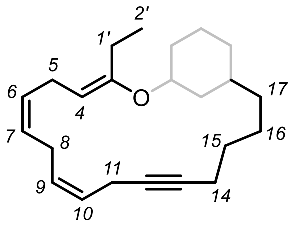


Figure 23 (a) ^{1}H NMR spectroscopic data (700 MHz, $CDCl_3$) for compound **91**; chemical shifts (in ppm) are followed by the multiplicity of the signal and the coupling constant in Hz. (b) Key nOe interactions for compound **91**, confirming the stereochemistry around the enol ether double bond.

The ^{1}H NMR spectroscopic data for the macrocyclic ring portion of compound **91** can be compared to that reported for the phacelocarpus 2-pyrone A **53** (Table 12).[94] Some portions of the compound (*e.g.* H-6 to H-14) match closely ($\Delta\delta$ < 0.1 ppm), but the largest chemical shift difference arises for the proton at H-4: δ 4.62 in the model system (**91**) against δ 5.11 in the natural compound (**53**), which suggests that the enol ether double bond is rather more electron deficient in the pyrone-containing system, but also therefore offers no insight into whether the correct stereochemistry has been assigned in the natural product.

Table 12 Comparison of ^{1}H NMR spectroscopic data for the aliphatic portion of compounds **91** and **53**.



Position[a]	***δ* (53) / ppm**[b,c]	***δ* (91) / ppm**[b]	**Δ*δ* / ppm**
4	5.11	4.62	−0.49
5	2.66	2.79	+0.13
6, 7	5.36	5.40	+0.04
8	2.77	2.86	+0.09
9, 10	5.36	5.45	+0.09
11	2.97	2.89	−0.08
14	2.20	2.16	−0.04
15	1.56	1.44	−0.12
16	1.88	1.67	−0.21
17	2.48	2.58	+0.10
1′	2.21	2.34	+0.13
2′	1.10	1.16	+0.06

[a]Numbering as for compound **91**. [b]For multiplets, the centrepoint of the range is quoted. [c]From reference [94] ($CDCl_3$, 360 MHz).

2.5 Summary

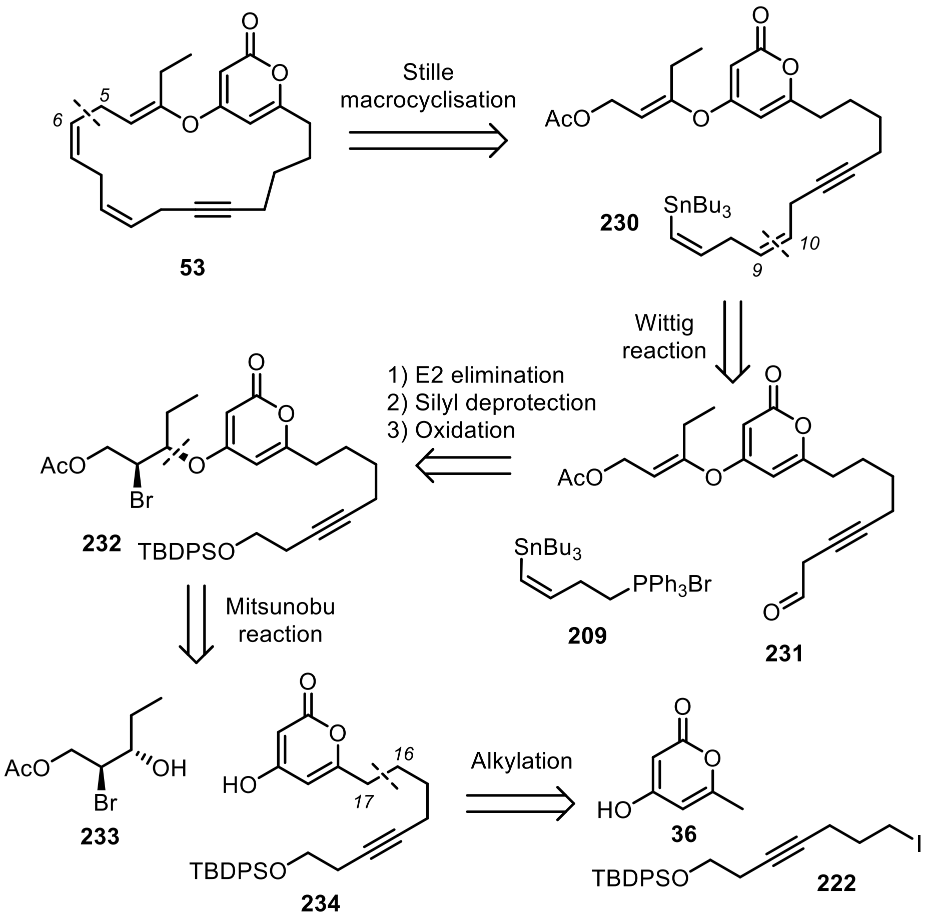
The successful synthesis of compound **91** has been achieved in 6.5% yield over 11 steps in the longest linear sequence. The key steps in assembling the challenging macrocyclic framework were a Pd-catalysed etherification reaction to construct the arylvinyl ether substructure, and sequential Wittig and Stille cross-coupling reactions using the novel phosphonium–stannane fragment **209** to build the skipped diene system. The effective use of the newly developed catalyst AsCat (**229**) has also been demonstrated. The efficient and convergent route established can serve as a proof of principle that macrocyclic polyenes containing 1,4-skipped-unsaturated functionality can be assembled in this way. This is demonstrated by the application of this synthetic strategy to the first total synthesis of phacelocarpus 2-pyrone A (**53**) which is discussed in Chapter 3.

Part of the work described in this chapter has been included in a publication (see Appendix 1).[192]

Chapter 3: Total Synthesis of Phacelocarpus 2-Pyrone A

3.1 Retrosynthetic Analysis

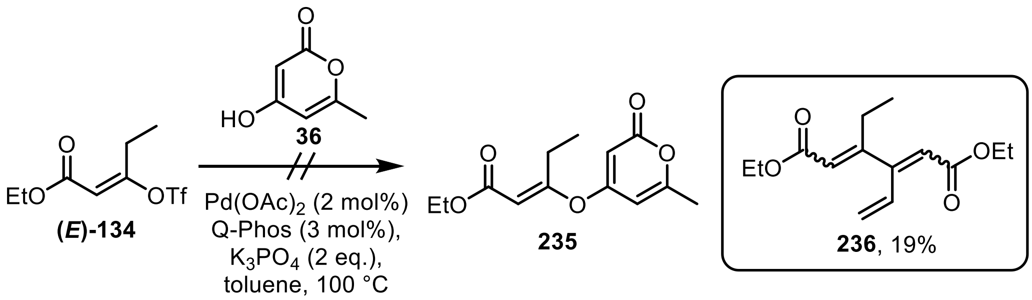
Based on the success of the second generation approach to the arene model compound **91** described in Chapter 2, a similar strategy was envisaged for the synthesis of the phacelocarpus 2-pyrone A (**53**), as shown in Scheme 63. The final steps of the synthesis would proceed exactly as in the model studies: a Stille macrocyclisation connecting C-5 and C-6, preceded by a (*Z*)-selective Wittig reaction forming a carbon–carbon double bond between C-9 and C-10. This would require two key fragments, the phosphonium salt (western fragment, **209**), synthesised previously (section 2.2.3, Chapter 2), and the pyrone compound (eastern fragment, **231**).



Scheme 63 Retrosynthetic analysis of natural product **53**.

Construction of the pyronylvinyl ether motif however, presented an additional challenge which would require exploration of some novel chemistry. An early attempt to use a

Buchwald–Hartwig etherification strategy (Scheme 64), as in the model system, led only to the isolation of an unexpected side product (**236**) and none of the desired enol ether (**235**). This could potentially arise from an elimination on triflate (*E*)-**134** followed by a Heck-type coupling another equivalent of the triflate, leading to the diester **236**. The stereochemistry of the trisubstituted double bonds could not be assigned with any certainty.

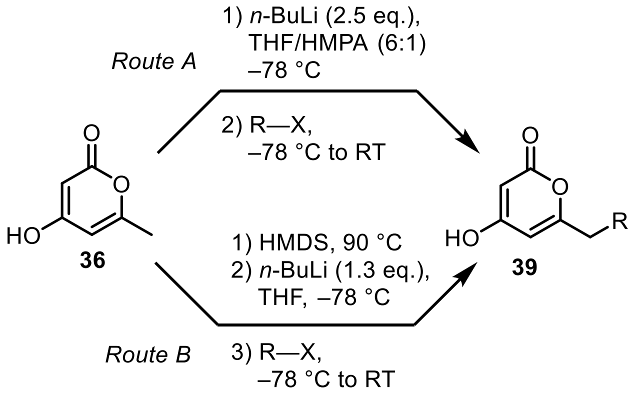


Scheme 64 Attempted Buchwald–Hartwig etherification with pyrone **36**.

An alternative method would therefore have to be found for the synthesis of the pyronylvinyl ether. The strategy chosen for this sought to build on the success of Dr M. J. Burns in previous studies,[105, 107] by using a Mitsunobu–elimination sequence (Scheme 63). The alkylated pyrone **234** was envisioned to undergo a Mitsunobu reaction with the secondary alcohol **233**, which should proceed with inversion at the alcohol centre, giving rise to the pyronyl ether **232**.[106] This could then undergo, in the presence of base, an E2 elimination forming the pyronyl vinyl ether substructure. Silyl deprotection and oxidation would give the required aldehyde for the Wittig coupling (**231**). The C-16–C-17 disconnection should be available using a reported method for the alkylation of 4-hydroxy-6-methyl-2-pyone (**36**).[75]

3.2 Synthesis of the Alkylated Pyrone

Two methods are reported by Hsung and co-workers for the alkylation of 4-hydroxy-6-methyl-2-pyrone (**36**).[75] One (route A) involves the treatment of the compound with excess *n*-BuLi in a mixture of THF and HMPA, followed by reaction with an alkyl halide. The second (route B) requires heating of the compound in HMDS to effect silylation of the hydroxyl group; fewer equivalents of *n*-BuLi are then required for the lithiation (Scheme 65).



Scheme 65 Alkylation methods of compound **36** reported by Hsung *et al.*

It was found in this case that the dilithiation strategy (route A) was far more effective than the silylation–lithiation method (route B). It was observed using *in situ* IR (ReactIR) studies that the dilithiation of the pyrone **36** with *n*-BuLi in the presence of HMPA was rapid with complete formation of the dilithium species (**36b**) within 10–12 min (Figure 24).

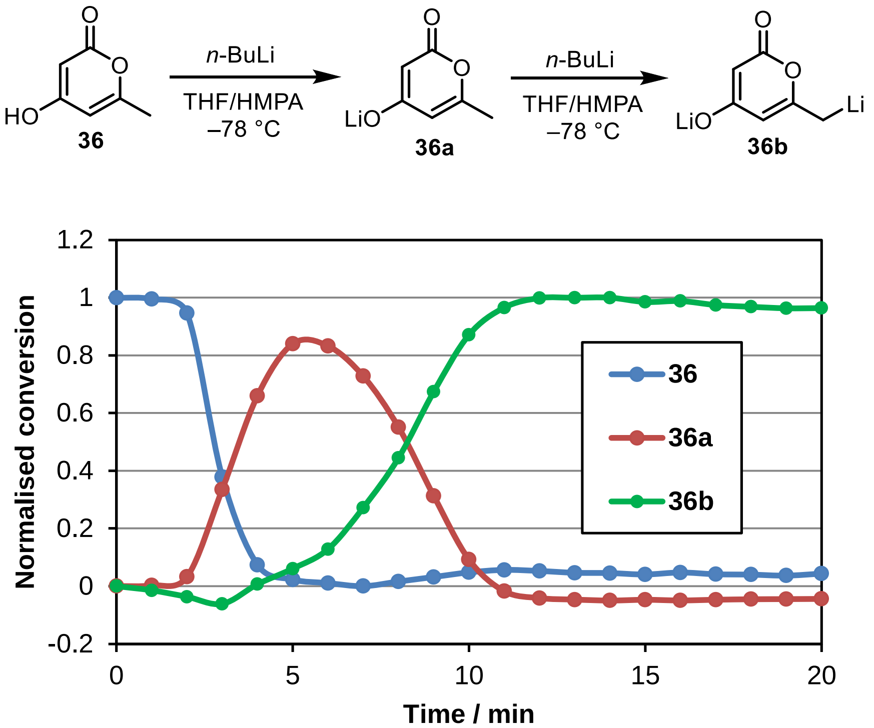
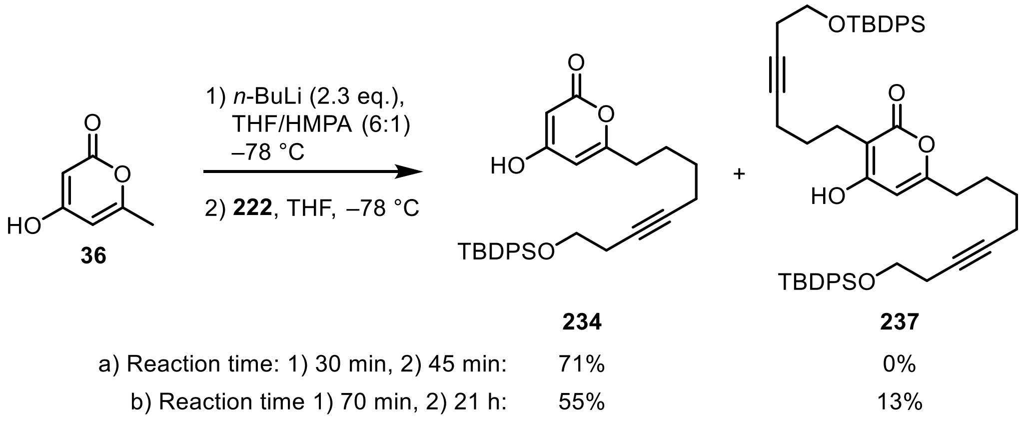


Figure 24 ReactIR data showing rapid dilithiation of pyrone **36**. Experiment conducted by M. Völkel.

Reaction of this dilithiated species with alkyl iodide **222** allowed isolation of the desired product **234** in 71% yield (Scheme 66). Extended reaction times or use of a large excess of *n*-BuLi led to formation of the dialkylated side product **237** (Scheme 66), presumably arising from competing lithiation on the pyrone ring. When the hydroxyl group on the pyrone was silylated with HMDS prior to lithiation and reaction with the alkyl iodide (route B), the same byproduct **237**, was also observed.

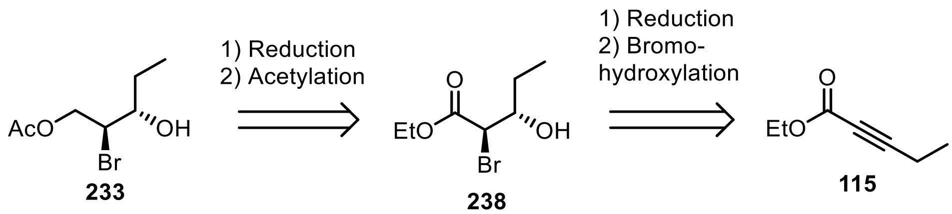


Scheme 66 Alkylation of 4-hydroxy-6-methyl-2-pyrone **36**, and the unwanted side product **237**.

3.3 Elimination Approach to Pyronylvinyl Ether

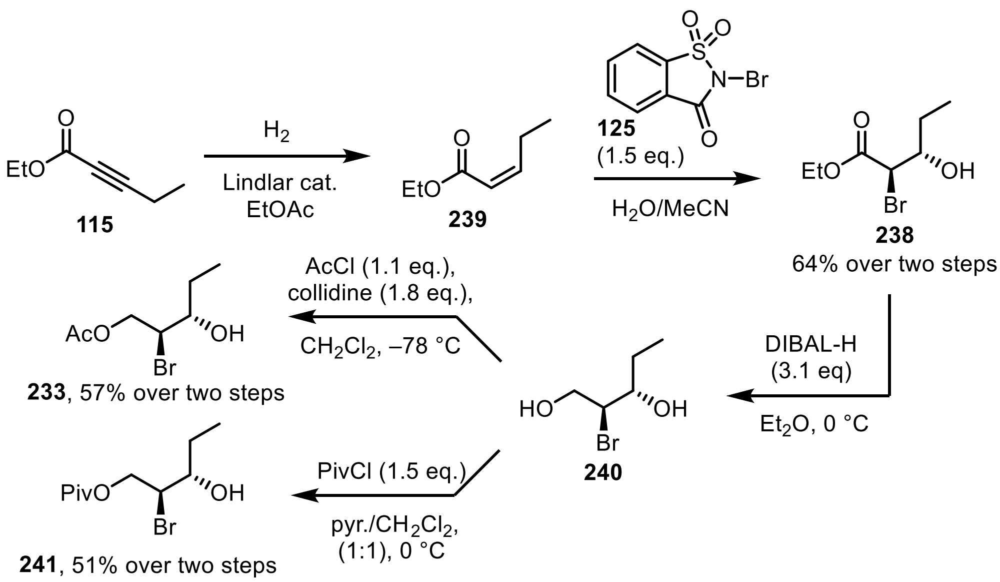
3.3.1 Synthesis of Secondary Alcohol

With the alkylated pyrone **234** in hand, attention turned to the synthesis of the required coupling partner for the planned Mitsunobu reaction. This was anticipated to be available from the bromohydrin ester **238** (Scheme 67) which is diastereomeric to the compound **127** synthesised as part of the model studies (see Chapter 2). In order to achieve the necessary relative stereochemistry, the starting material would be the (*Z*)-pentenoate which would in turn come from a hydrogenation of the commercially available pentynoate **115**.



Scheme 67 Planned retrosynthesis of compound **233**.

The synthesis proceeded as planned, as shown in Scheme 68. Reduction of ethyl 2-pentynoate (**115**), according to a literature procedure,[193] was followed by reaction with *N*-bromosaccharin, affording the bromohydrin **238** in 64% yield over two steps as a single diastereomer. This could be reduced by treatment with excess DIBAL-H, and the resulting diol could be selectively acetylated[194] or pivaloylated[195] on the primary hydroxyl only, both following literature procedures.



Scheme 68 Forward synthesis of compounds **233** and **240**.

For ester **238**, the vicinal coupling constant ($^3J_{H\text{–}H}$ = 4.2 Hz) observed between the H_a and H_b (Figure 25) was found to differ from that for bromohydrin **127**, derived from the (*E*)-alkenoate ($^3J_{H\text{–}H}$ = 7.2 Hz), supporting the assignment of different relative stereochemistry.

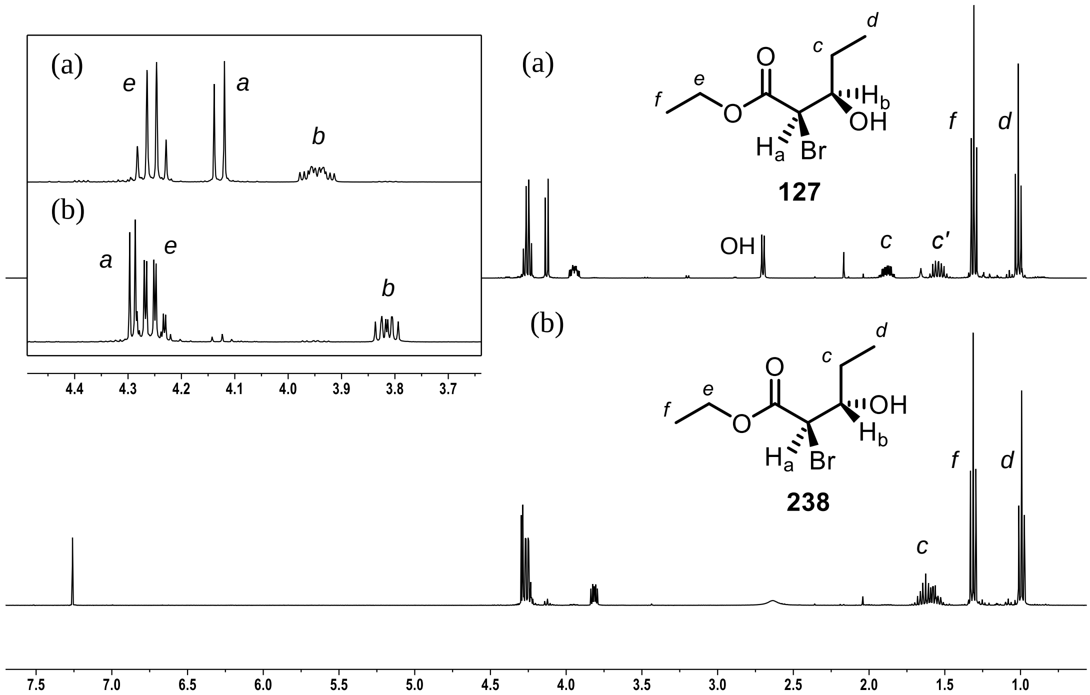
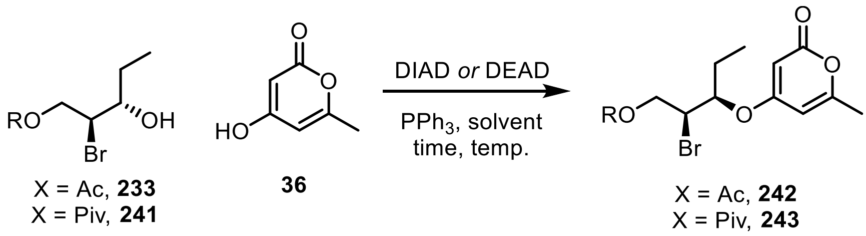


Figure 25 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of diastereomeric compounds (a) **127** and (b) **238**. Inset: expansion of the 3.7–4.4 ppm region.

3.3.2 Mitsunobu Reactions

Initial screening of the Mitsunobu reaction of secondary alcohol **233** with 4-hydroxy-6-methyl-2-pyrone **36** under literature conditions[106] led to no formation of product **242** (entry 1, Table 13). An extensive screening was subsequently carried out, selected examples of which are shown in Table 13 (for full table, see Appendix 2). Heating the reaction to 40 °C in dichloromethane afforded partial conversion (entry 2, Table 13), but switching to the more polar solvents THF or DMF completely suppressed the formation of product (entries 3 and 4, Table 13). The use of toluene, however, led to improved conversion (entry 5, Table 13). Switching from DIAD to the more polar DEAD allowed more straightforward removal of the hydrazine byproduct and facilitated the isolation of the pyronyl ether **242** (entry 6, Table 13). Similar conversions could also be obtained at RT (entry 7, Table 13); in one case a quantitative conversion was obtained (entry 8, Table 13), although this could not be replicated on subsequent attempts and the reasons for this result remain unclear. The use of neopentyl alcohol as an additive led to no product formation (entry 9, Table 13).[196] Employing DMEAD (Figure 26), a more reactive and polar replacement for DIAD and DEAD,[197] led to no improvement in conversion (entry 10, Table 13). The pivalate substrate **241** could also be used in the reaction; its reduced polarity with respect to the acetate led to easier purification of the corresponding pyronyl ether **243**. Adding the reagents at low temperature before slowly warming the reaction mixture to RT was found to be an effective strategy, leading to the isolation of **243** in good yield (entry 12, Table 13).

Table 13 Screening of conditions for Mitsunobu reaction.



Entry	Reagents	R	Time / h	Solvent	Temp. / °C	Conv. / %[a, b]
1	DIAD (1.5 eq.), PPh_3 (1.5 eq.)	Ac (1.5 eq.)	6	CH_2Cl_2	RT	0
2	DIAD (1.5 eq.), PPh_3 (1.5 eq.)	Ac (1.5 eq.)	24	CH_2Cl_2	40	50
3	DIAD (1.2 eq.), PPh_3 (1.2 eq.)	Ac (1.1 eq.)	23	THF	50	0
4	DIAD (1.2 eq.), PPh_3 (1.2 eq.)	Ac (1.1 eq.)	19	DMF	40	0
5	DIAD (1.5 eq.), PPh_3 (1.5 eq.)	Ac (1.5 eq.)	24	toluene	40	62
6	DEAD (1.9 eq.), PPh_3 (2 eq.)	Ac (2 eq.)	24	toluene	40	53 (45)
7	DEAD (2.2 eq.), PPh_3 (2 eq.)	Ac (2 eq.)	23	toluene	RT	56
8	DEAD (2 eq.), PPh_3 (2 eq.)	Ac (2 eq.)	21	toluene	RT	100
9	DEAD (1.1 eq.), PPh_3 (1.1 eq.), NpOH (0.5 eq.)	Ac (1.1 eq.)	24	toluene	40	0
10	DMEAD (1.2 eq.), PPh_3 (1.2 eq.)	Ac (1.2 eq.)	24	toluene	RT	50
11	DEAD (1.5 eq.), PPh_3 (1.5 eq.)	Piv (1.5 eq.)	23	toluene	RT	32
12	DEAD (2 eq.), PPh_3 (2 eq.)	Piv (2 eq.)	25	toluene	–78 to RT	69 (66)

[a]As judged by ^{1}H NMR spectroscopy. [b]Yields of isolated product in parentheses.

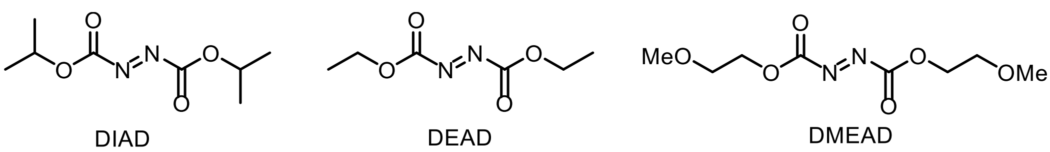
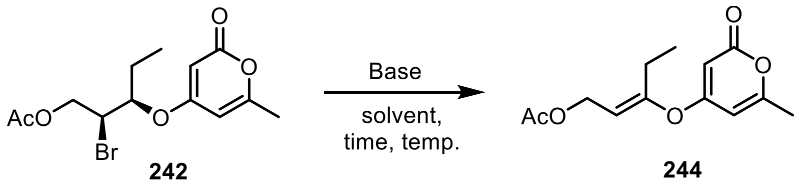


Figure 26 Structures of azodicarboxylates used in Table 13.

3.3.3 Elimination Reactions

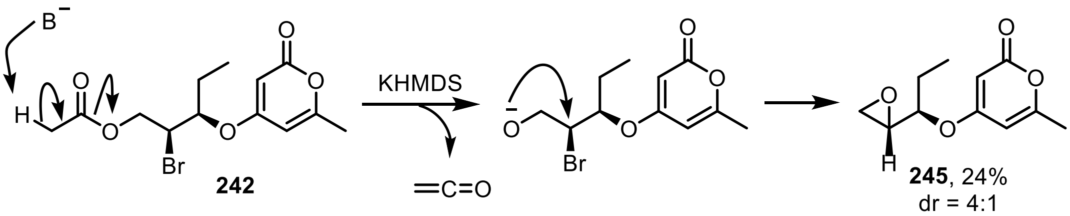
With the required ethers **242** and **243** in hand, a screening of bases and conditions was carried out for the E2 elimination reaction. Although previous studies have found eliminations on similar systems to be efficient,[105] heating bromide **242** with two equivalents of DBU in THF at 70 °C led to no reaction and recovery of starting material only (entry 1, Table 14). Switching the solvent to dioxane and increasing the temperature to 100 °C led to little or no formation of product (entries 2–4, Table 14). When five equivalents of base were employed (entry 5, Table 14), complete consumption of starting material was observed, but only a small amount (17%) of product **244** could be isolated, suggesting that substrate decomposition was a significant problem. Despite the low yields obtained, it was gratifying to note that the product was obtained as a single stereoisomer suggesting that the elimination process is stereospecific as anticipated. Reaction also took place at 90 °C in toluene (entry 6, Table 14), but afforded product **244** in a similarly poor yield (13%). A number of other bases led to decomposition or no reaction (entries 7–9, Table 14), with the exception of KHMDS, which gave partial conversion to the unexpected side product **245**, which was isolated in 24% yield, in a dr of 4:1 as judged by ^{1}H NMR spectroscopic analysis. The formation of this compound could be envisaged to arise from base-mediated removal of the acetate group,[198] with formation of ketene, followed by intramolecular S_N2 reaction (Scheme 69); on this basis the major diastereomer was assumed to be the one depicted.

Table 14 Various attempts to effect elimination of bromide **242**.



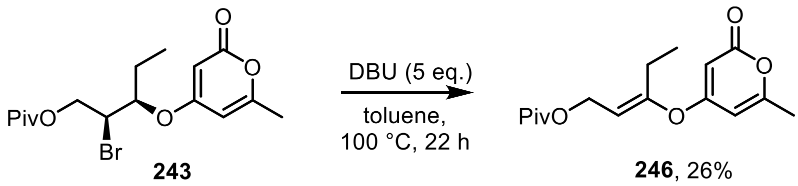
Entry	Base	Time / h	Solvent	Temp / °C	Reaction outcome[a]
1	DBU (2 eq.)	23	THF	70	N. R.[b]
2	DBU (1.5 eq.)	22	dioxane	100	N. R.[b]
3	DBU (2 eq.)	6	dioxane	100	trace[b]
4	DBU (3 eq.)	19	dioxane	100	trace[b]
5	DBU (5 eq.)	24	dioxane	100	17%[c]
6	DBU (5 eq.)	24	toluene	90	13%[c]
7	NaOMe	16	MeOH	RT	dec.[d]
8	*t*-BuOK (1.05 eq.)	24	THF	RT → 60	N. R.[b]
9	DIPEA (5 eq.)	26	dioxane	100	N. R.[b]
10	KHMDS (1.1 eq.)	16	THF	RT	Formation of **245**[d]

[a]As determined by ^{1}H NMR spectroscopy. [b]Recovery of starting material confirmed by ^{1}H NMR spectroscopy. [c]Yield of isolated product following chromatography in silica gel. [d]See Scheme 69.



Scheme 69 Proposed mechanism for the formation of side product **245**.

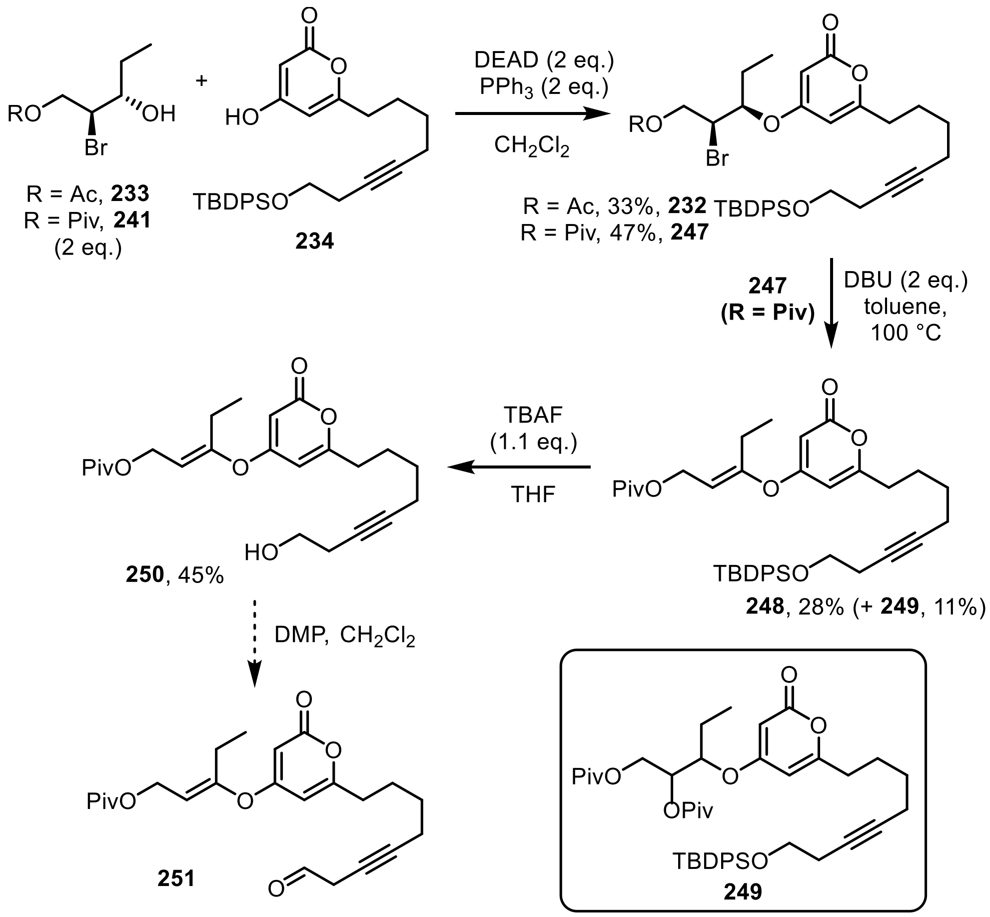
The possibility of a base-mediated removal of the acetate group during the elimination reaction and concomitant formation of side products led us to consider elimination of a substrate bearing a more stable pivalate group in place of the acetate. When the pivalate-derived bromide **243** was treated with five equivalents of DBU at 100 °C in toluene (Scheme 70), the desired product (**246**) could be isolated in a 26% yield with no recovery of starting material, suggesting that side reactions and decomposition remain problematic for this transformation.



Scheme 70 Elimination reaction of allylic pivalate **243** with DBU.

3.3.4 Approach Towards Eastern Fragment

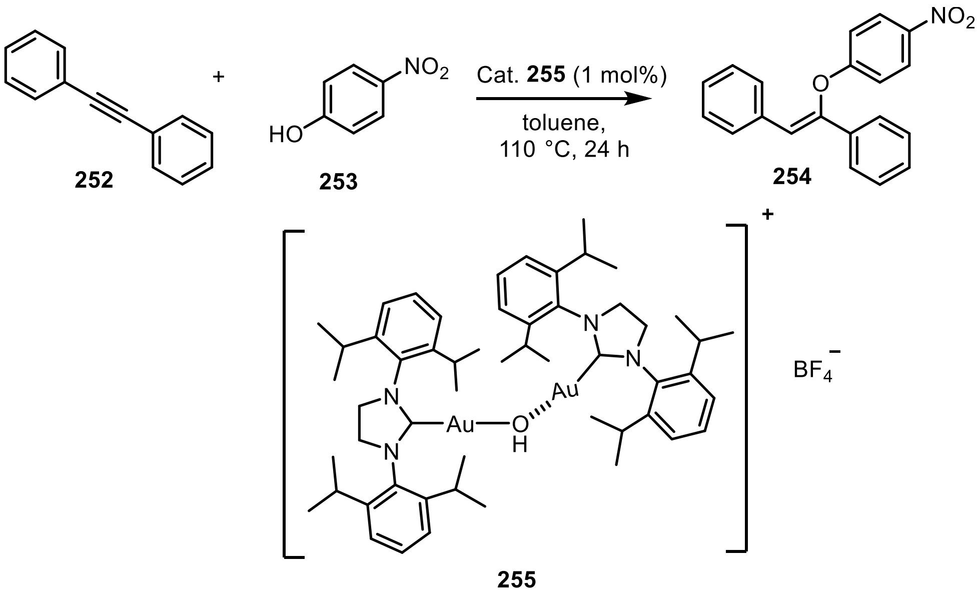
Despite the low isolated yields obtained in the elimination attempts of the simple systems above, it was decided to go forward and attempt the same process with the alkylated pyrone **234**. The Mitsunobu reaction was successful with both the acetate- and pivalate-derived alcohols **233** and **241**, affording the brominated ethers **232** and **247** respectively (Scheme 71). The elimination reaction with the acetate **232** gave a complex mixture from which no product could be isolated; however, reaction with the pivalate **247** did lead to the formation of isolable product (**248**) in 28% yield, but along with the unexpected bis-pivalate **249** in 11% yield, the presence of which suggests decomposition and side reactions remain problems for this chemistry. The vinyl ether **248** could then be taken on and deprotected under standard conditions to give alcohol **250**. Attempts to oxidise the small amount of **250** obtained did not lead to the isolation of any of the desired aldehyde **251**. Due to the successive low yields obtained in this synthetic sequence, only a very limited amount of material could be carried through to this stage. These limitations meant that this approach was abandoned in favour of the Au-catalysis methodology described in Section 3.4.



Scheme 71 Synthesis of vinyl ether **250**.

3.4 Addition Approach to Pyronylvinyl Ether

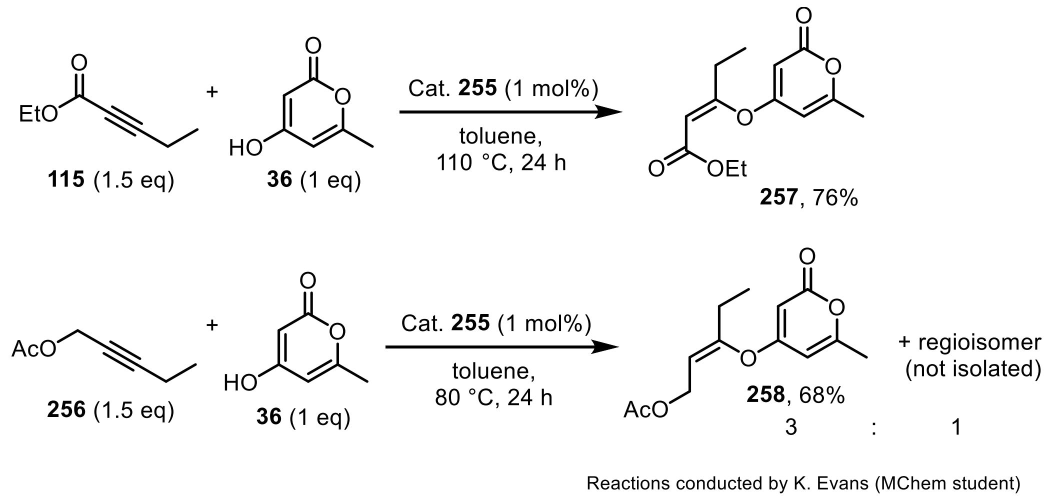
Following the difficulties encountered in the Mitsunobu–elimination approach to the eastern fragment of the natural product, our attention was drawn to a report by Nolan and co-workers, which described the use of cooperative Au^{I} catalysis to facilitate the addition of phenols to internal alkynes to afford (*Z*)-enol ethers.[199] First reported by Nolan in 2010,[200] the unusual dinuclear $[(Au(IPr))_2(\mu\text{-OH})][BF_4]$ complex (**255**) is able to catalyse the reactions efficiently at low catalysts loadings (0.5–1 mol%) and with highly acidic phenols (*e.g.* Scheme 72).



Scheme 72 The addition of acidic phenols such as **253** to internal alkynes, as reported by Nolan and co-workers.[199] (Note: the NHC ligand possesses nitrogen stabilisation at the carbene centre – not shown).

The methodology has since been combined with Pd catalysis to allow one-pot access to benzo[*c*]chromenes and benzo[*b*]furans,[201] and expanded to include benzylic and aliphatic alcohols.[202]

It was postulated that this methodology could be applied to the synthesis of pyronylvinyl ethers in a similar fashion. Accordingly, when 4-hydroxy-6-methyl-2-pyrone (**36**) and alkynes **115** and **256** were reacted with complex **255** in toluene, compounds **257** and **258** were isolated in 76% and 68% yields respectively (Scheme 73). The regioselectivity for compound **257** was essentially complete, whilst for compound **258**, a 3:1 ratio of regioisomers was observed, although the minor isomer was not isolated. This methodology was subsequently expanded and found to be highly applicable to a range of alkynes and 2-pyrone derivatives.[203]



Scheme 73 Examples of reaction of 2-pyrone **36** with alkynes **115** and **256**.

As reported,[199, 202] the (*Z*)-isomer was the only isolable product in each reaction. This could be confirmed by noting, for example in compound **258**, the $^4J_{H\text{–}H}$ = 1.3 Hz between the vinyl ether proton (H_b δ 5.37) and the CH_2 of the ethyl group (H_c δ 2.22) in the ^{1}H NMR spectrum, a coupling which was absent in the (*E*)-isomer (**244**) synthesised by the elimination route (Figure 27).

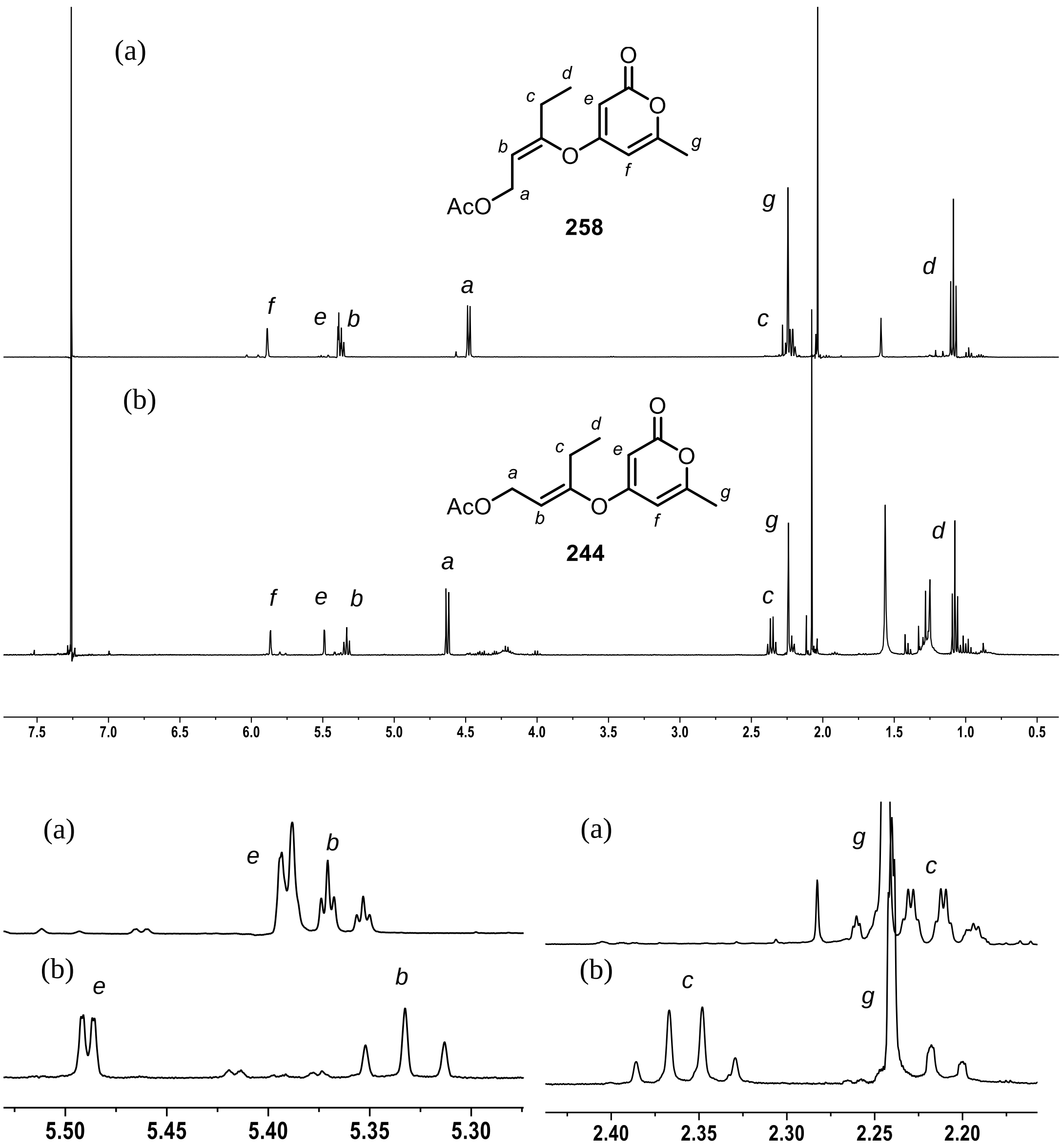
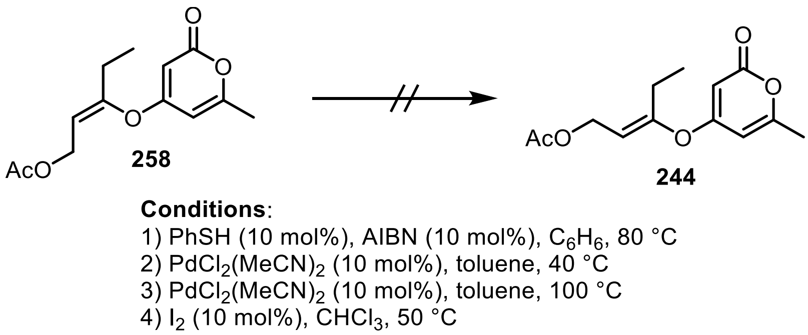


Figure 27 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of (a) **258** and (b) **244** with expansions of the alkene and CH_2 regions.

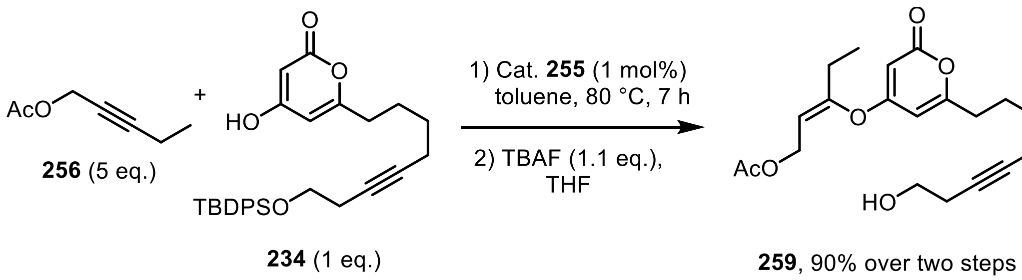
The total synthesis of the reported structure of compound **53**, however, would require access to the (*E*)-enol ether. A number of attempts were made to isomerise the double bond in compound **258** (conditions 1–4, Scheme 74), but no isomerisation was detected under any of the conditions tested.



Scheme 74 Attempted isomerisations of **258** into **244**.

It was, however, proposed that as for the arene model system, isomerisation might be observed during the Stille coupling with the allylic acetate and, moreover, this isomerisation might be encouraged by using a higher temperature for the final cyclisation reaction. If the two geometrical isomers formed in this step were found to be separable, this would provide a viable route to both isomers of the natural product, allowing final confirmation of the stereochemistry around the enol ether double bond, an issue about which there remains uncertainty.

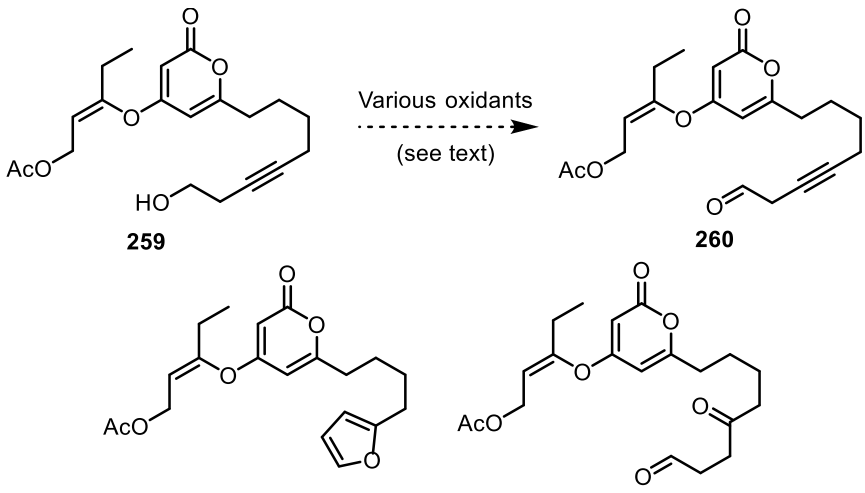
As such, the alkylated pyrone **234** was reacted with alkyne **256** using the Au catalyst **255**. The acetate was used in excess (five equivalents) to minimise possible side reactions resulting from the pyrone reacting with the alkyne moiety present on the side chain. Gratifyingly, under these conditions the reaction proceeded smoothly, giving a regioisomeric ratio of 10:1 (by ^{1}H NMR spectroscopy) in favour of the desired compound; deprotection with TBAF followed by flash chromatography on silica gel led to the isolation of the desired homopropargylic alcohol **259** in 90% yield over two steps (Scheme 75). It is worth noting that, although run in technical grade toluene under air, this reaction appears to be sensitive to trace impurities in either the acetate or pyrone, the presence of which can lead to reaction failure and the formation of little or no product. More investigation is required to determine the exact nature of this effect.



Scheme 75 Synthesis of (*Z*)-vinyl ether **259**.

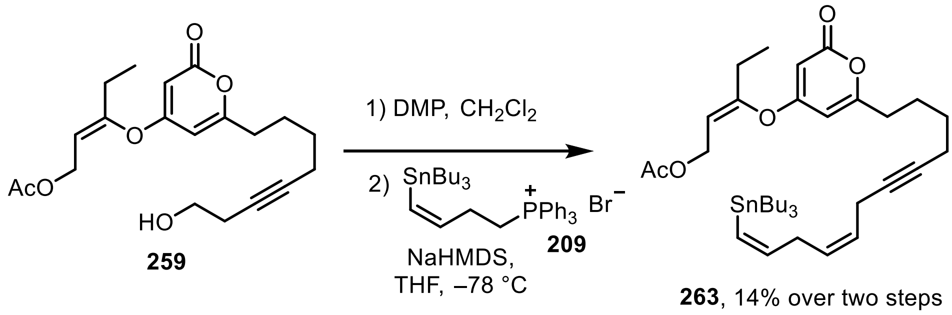
3.5 Oxidation, Wittig Coupling and Cyclisation

Initial attempts to oxidise the alcohol **259** to an aldehyde under the Dess–Martin conditions used in the model studies (Chapter 2) were not straightforward, and the high polarity of the pyrone compound meant that it was difficult to separate the desired aldehyde cleanly from excess DMP and DMP byproducts at the end of the reaction; decomposition and side-product formation was also noted, in particular furan **261** was isolated from one reaction in 17% yield (Scheme 76). A number of other oxidants were also tested including PDC and TPAP, with all leading to decomposition, and PCC, which led to the formation of the 1,4-dicarbonyl compound **262** in 57% yield.



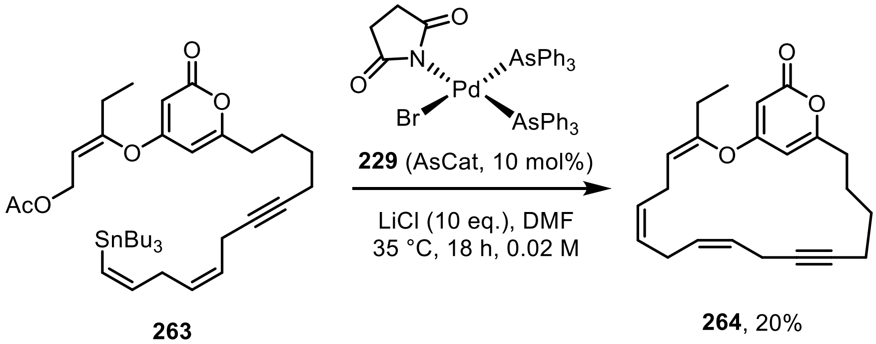
Scheme 76 Attempted oxidation of alcohol **259** and resulting side products.

It was noted that the dicarbonyl **262** is in fact a precursor compound to the furan **261**, and this suggested that the major side reaction was hydration of the alkyne. This was presumably catalysed by residual gold remaining from the alkyne addition step; Au-catalysed hydration of alkynes is known with catalyst loadings as low as 10 ppm.[204] Accordingly, a thiourea-based resin (Quadrapure-TU), which is designed to scavenge metal atoms, was added to the crude reaction mixture immediately after the Au-catalysed addition step. Deprotection and purification by flash chromatography as before gave an alcohol (**259**) which could be cleanly oxidised to the aldehyde **260**. This was used immediately in the Wittig coupling with stannane–phosphonium salt **209** (Scheme 77). This reaction did not lead to clean formation of product, however, and the stannane **263** could only be isolated in 14% yield over two steps. The low yield in this reaction was attributed to the sensitive nature of the aldehyde coupling partner and accompanying decomposition during the reaction.



Scheme 77 Oxidation and Wittig coupling of alcohol **259**.

With the cyclisation precursor in hand, the Stille cross-coupling reaction was carried out under the conditions used in the model system (Scheme 78). A higher temperature of 35 °C was used in order to try and encourage any isomerisation of the enol ether bond; the reaction was thus complete (as judged by consumption of **263** by TLC) in 18 h. Preparative TLC purification of the crude reaction mixture led to the isolation of a small amount of the cyclised product **264** (20% yield), which appeared to be present as a single isomer.



Scheme 78 Cyclisation of **263** to give macrocycle **264**.

3.6 Characterisation and Structural Reassignment

When a ^{1}H NMR spectrum of **264** was acquired in C_6D_6, the $^{4}J_{H\text{–}H}$ = 1.2 Hz between H-4 and H-1′ was clearly apparent as in the precursor compound (**263**), suggesting that the (*Z*)-geometry had been retained in the macrocycle. A 1D nOe experiment irradiating H-4 led to a 2.1%, 1.7% and 1.6% enhancement of protons H-5, H-1′ and H-2′ respectively (Figure 28 (b)). This can be compared to the reported nOe experiments on other members of the phacelocarpus pyrone family (Figure 28 (c)). The (*E*)-4-pyrone compound **52** gave no enhancement of the H-1′ protons on irradiation at H-4,[94] whereas the two compounds **50** and **57**, both assigned a (*Z*)-geometry, gave an interaction between H-4 and the H-2′ methyl group.[96] No nOe experiments are reported for the target natural product **53** (Figure 28 (a)). It is also worth noting that the model compound, with a confirmed (*E*)-geometry, had no

NOESY interaction between H-4 and H-1′ or H-2′ (see Chapter 2). These comparisons all suggest that the (*Z*)-geometry of synthetic **264** can be assigned with confidence.

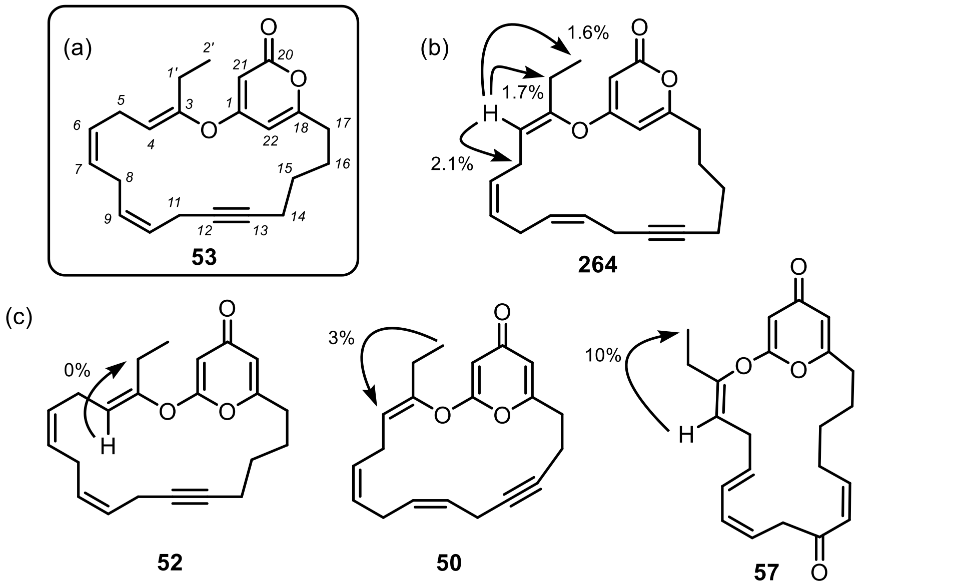
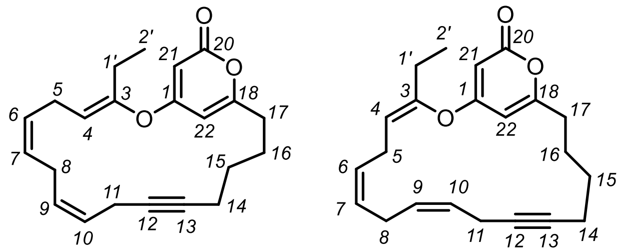


Figure 28 (a) Reported structure of natural compound **53** (no nOe experiments reported); (b) one-dimensional nOe enhancements measured for compound **264** and (c) those reported for compounds **52**, **50** and **57**.[94, 96]

A full NMR spectroscopic characterisation of the compound was run in $CDCl_3$ solution, including COSY, HSQC and HMBC spectra (see Appendix 5 for a full list of correlations). Pleasingly, the data were found to match very closely to those reported for the natural compound, with the ^{13}C NMR spectrum (referenced to $CDCl_3$ = 77.0 ppm) having all of the signals within 0.1 ppm of those reported (Table 15). Note that the carbon signals were only tentatively assigned in the original report,[94] and so have been reassigned here with confidence based on HSQC and HMBC experiments.

Table 15 Comparison of reported ^{13}C NMR shifts for the natural compound with those for synthetic **264**.

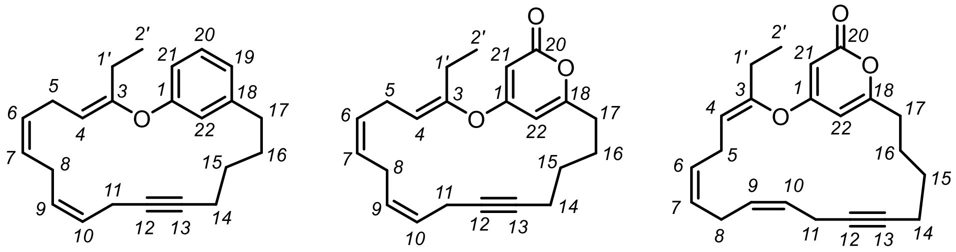


Position	*δ* (53, natural)[a] / ppm	*δ* (53, natural), reassigned / ppm	*δ* (264, synthetic)[b] / ppm	Δ*δ* / ppm
1	169.0	165.1	165.1	0
3	151.0	151.0	151.1	+0.1
4	89.6	114.2	114.3	+0.1
5	18.1	23.8	23.8	0
6	124.4	126.6	126.7	+0.1
7	126.6	128.4	128.5	+0.1
8	23.8	25.3	25.3	0
9	128.4	130.5	130.6	+0.1
10	130.5	124.4	124.4	0
11	25.0	16.9	16.9	0
12	78.9	78.9	79.0	+0.1
13	79.3	79.3	79.4	+0.1
14	25.3	18.1	18.2	+0.1
15	25.5	27.3	27.3	0
16	27.3	25.0	25.0	0
17	32.3	32.3	32.4	+0.1
18	165.1	166.9	167.0	+0.1
20	166.9	169.0	168.9	−0.1
21	114.2	89.6	89.7	+0.1
22	99.0	99.0	99.0	0
1′	16.9	25.5	25.5	0
2′	11.0	11.0	11.1	+0.1

[a]From reference [94] (50 MHz). [b]Referenced to $CDCl_3$ = 77.0 ppm (175 MHz).

Similarly, almost all of the chemical shifts in the ^{1}H NMR spectrum ($CHCl_3$ = 7.24 ppm) of **264** are in very good agreement ($\Delta\delta$ < 0.1 ppm) of the natural compound, with the exception of the two hydrogens on the pyrone ring at positions C-21 and C-22, which deviate by 0.20 and 0.12 ppm respectively (Table 16). An IR band at 1733 cm^{-1} in the synthetic compound confirms the presence of a 2-pyrone, so it is unclear why those peaks in particular exhibit such a large deviation. The agreement for the aliphatic portion of the compound is also much closer than that for the aromatic model system **91**, which has the opposite (*E*)-stereochemistry to **264** around the enol ether double bond.

Table 16 Comparison of reported ^{1}H NMR shifts for natural **53** with those of synthetic **264** and the aromatic model system **91**.



91
model system

53
reported structure of natural compound

264
synthetic

Position	δ (91) / ppm[a,b]	$\Delta\delta$ / ppm	δ (53, nat.)[b,c] / ppm	$\Delta\delta$ / ppm	δ (264, synth.)[a,b] / ppm
4	4.60	−0.51	5.11	+0.03	5.14
5	2.77	+0.11	2.66	−0.02	2.64
6, 7	5.38	+0.02	5.36	+0.05	5.41
8	2.84	+0.07	2.77	+0.02	2.79
9, 10	5.43	+0.07	5.36	+0.05	5.41
11	2.87	0	2.87	−0.01	2.86
14	2.14	−0.06	2.20	−0.03	2.17
15	1.42	−0.14	1.56	+0.01	1.57
16	1.65	−0.23	1.88	−0.09	1.79
17	2.56	+0.12	2.48	+0.02	2.50
21	-	-	5.20	+0.20	5.40
22	-	-	5.89	+0.12	6.01
1′	2.32	+0.11	2.21	−0.04	2.17
2′	1.14	+0.04	1.10	−0.05	1.05

[a]Referenced to $CHCl_3$ = 7.24 ppm (700 MHz); [b]For multiplets, the centrepoint of the range is quoted. [c]From reference [94] (360 MHz).

The very close agreement of the NMR spectroscopic data, along with the tentative fashion in which the stereochemistry of **53** was originally assigned (see Chapter 1), is compelling enough to suggest that compound **264** possesses the same structure as the natural compound, which, given the confirmation of the (*Z*)-stereochemistry, implies that the incorrect geometrical isomer has been proposed for the natural product.

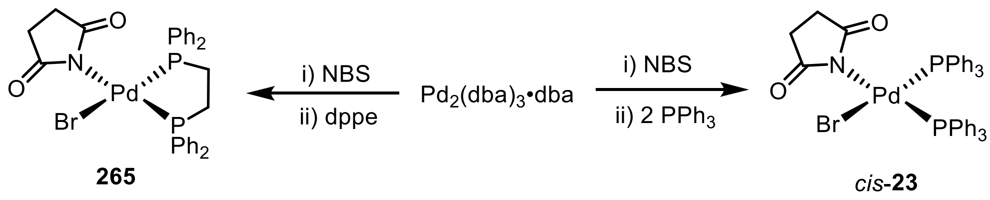
3.6 Summary

The first total synthesis of phacelocarpus 2-pyrone A has been completed in 1.4% overall yield over nine steps in the longest linear sequence. Full structural characterisation and confirmation of stereochemistry have been carried out, and, in light of the very close agreement with the reported data, this has allowed a stereochemical reassignment of the natural compound to the (*Z*)-isomer about the trisubstituted double bond. The chemistry employed in the synthesis has built upon the successful construction of a macrocyclic aromatic model compound described in Chapter 2, employing the same retrosynthetic disconnections and synthetic strategy. A novel Au-catalysed method for the formation of (*Z*)-pyronyl enol ethers has been utilised, along with the sequential Wittig reaction and Stille cross-coupling used to complete the macrocyclic ring.

Chapter 4: Air Effects in Stille Couplings

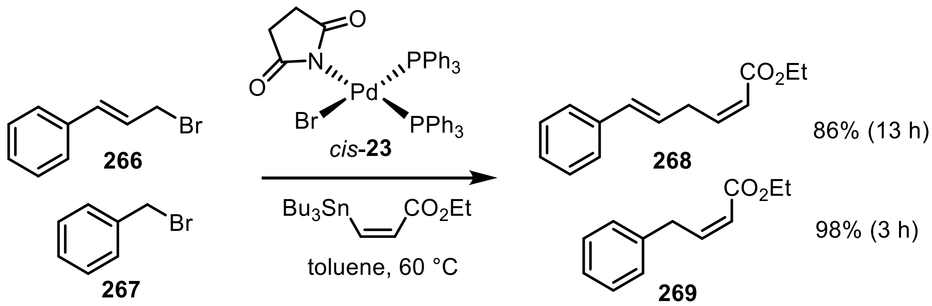
4.1 Introduction to Succinimide Pd Catalysts

In 1999 Serrano and co-workers first reported the facile oxidative addition of *N*-bromosuccinimide to Pd(0) and Pt(0) precursor complexes, giving rise to the corresponding air-stable imidate complexes such as **265** and *cis*-**23** (Scheme 79).[49]



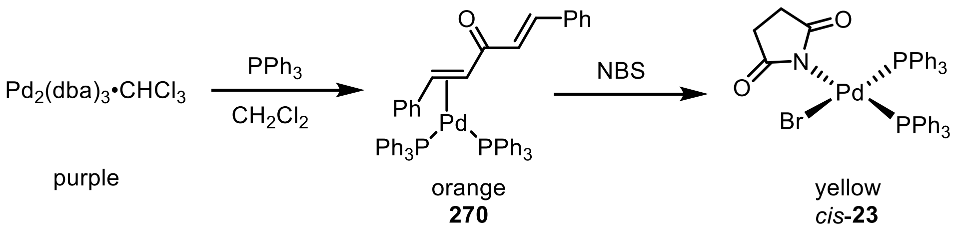
Scheme 79 Serrano's original syntheses of complexes **265** and *cis*-**23**.

Following this initial report, during studies towards the total synthesis of inthomycin C,[205] Fairlamb, Taylor and co-workers discovered in 2003 that the presence of trace amounts of *N*-bromosuccinimide in their starting materials facilitated Stille couplings with benzyl bromides.[53-54] Further investigation revealed that the preformed complex *cis*-**23** was an efficient precatalyst for a range of benzylic and allylic Stille couplings (*e.g* Scheme 80).[50, 53]



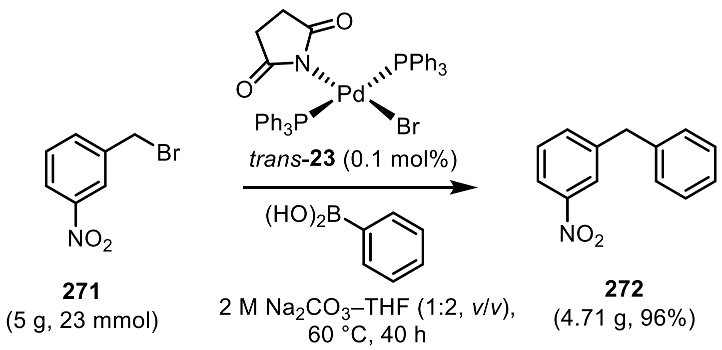
Scheme 80 Application of complex *cis*-**23** in the Stille reaction.[50]

A reproducible method for the synthesis of *cis*-**23** was found: treatment of the precursor complex $Pd_2dba_3{\cdot}CHCl_3$ with two equivalents of PPh_3 per Pd forms the $Pd(\eta^2\text{-dba})(PPh_3)_2$ intermediate **270** (Scheme 81), addition of NBS leads to oxidative addition into the N–Br bond and formation of the desired complex *cis*-**23**.[53]



Scheme 81 Synthesis of *cis*-**23**.

The same group reported that the isomeric complex *trans*-Pd(*N*-succ)Br(PPh_3)$_2$ (*trans*-**23**) can also be used as an efficient catalyst for both benzylic and aryl Suzuki–Miyaura couplings on multi-gram scale, with catalyst loadings as low as 0.1% (Scheme 82).[51-52, 206] *Trans*-**23** has subsequently been commercialised by Sigma-Aldrich (catalogue number 643742).



Scheme 82 Application of complex *trans*-**23** in the Suzuki–Miyaura reaction.

The intriguing activity of these catalysts is proposed to be due to the presence of the succinimide ligand. Imidate ligands such as this have similar electronic properties to halide ligands, but can coordinate to metals in a variety of ways (Figure 29),[207] and it is thought that these different coordination modes may be able to stabilise catalytic intermediates in a way that other anionic ligands cannot. Fairlamb, Serrano and co-workers have prepared an extensive library of imidate-containing Pd complexes (see examples, Figure 29), in an effort to exploit the properties imparted by these ligands, and found that many of them exhibit remarkable catalytic activity in a number of different cross-coupling reactions.[53, 208-216]

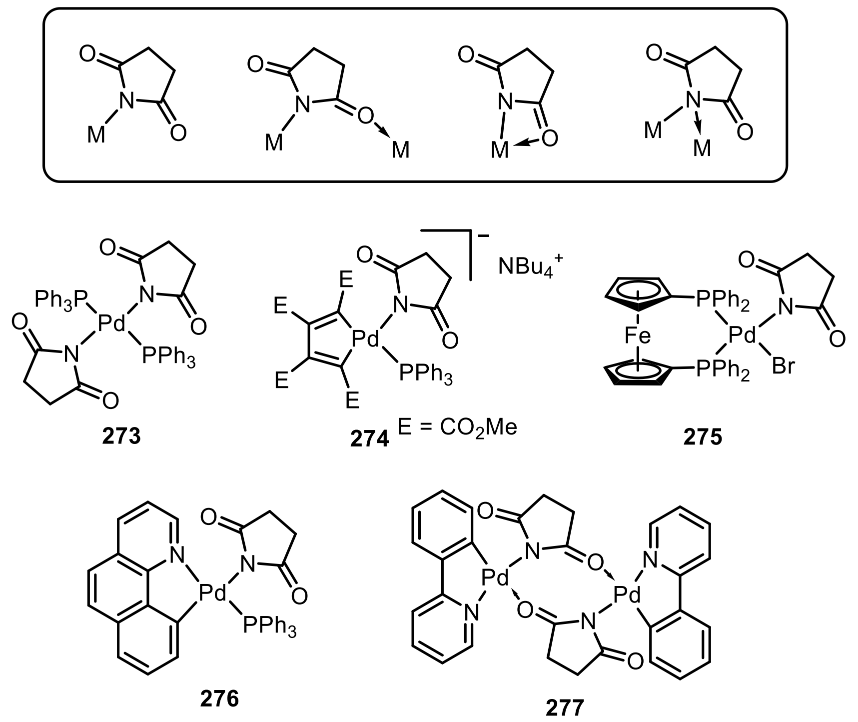


Figure 29 Above: potential coordination modes of imidate ligands; Below: examples of imidate-containing Pd complexes (**273**–**277**).

Cis- and *trans*-**23** remain two of the most thoroughly examined imidate complexes in terms of scope and reactivity, but despite these impressive results, a number of aspects of these two catalysts remain unexplored. It had been noted during previous mechanistic studies that the activity of the catalyst is somewhat sensitive to the presence of air, and that the colour of the reaction mixture is also dependent on exposure to air. If reactions were performed under rigorously inert conditions then the reactions remained yellow, but if exposed to air they rapidly turned black. Moreover, it was noted that some reactions actually *required* a trace amount of air to initiate catalyst turnover, *i.e.* providing a competent species that can enter into the catalytic cycle (see Chapter 2). Similar observations in relation to the presence or absence of trace air have been recently reported for a $Pd(PPh_3)_4$ system employed in the Stille coupling (also noted in previous unpublished studies within the group).[217] Given these intriguing preliminary observations, it was decided to undertake a systematic study of the effect of air on the catalytic ability of the complexes.

4.2 Preliminary Studies

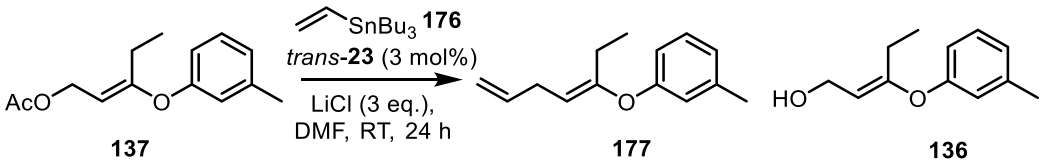
Following the unusual observations made during the target-oriented synthesis discussed earlier (see Chapter 2), whereby a trace amount of air was required to activate the catalyst and allow the reaction to proceed, an examination of the amount of air needed to initiate the same model reaction was carried out (Table 17). All reactions were carried out with *trans*-

23 as the Pd source, at the same reaction scale (0.21 mmol **137**, 6.2 μmol Pd) using an identically sized Schlenk tube as the reaction vessel (see Figure 30(a)) and with equivalent stirring rates.

As had been observed previously, when the reaction was carried out in the absence of air, little conversion into product **177** was observed (entry 1, Table 17). Warming the reaction mixture led to improved conversion into the product (entries 2 and 3, Table 17), but also to isomerisation of the trisubstituted enol ether double bond (in all other entries, E:$Z \geq 9$:1). Removal of the reaction vessel stopper for 5 seconds (with no flow of N_2) led to complete consumption of the starting material (**137**), and concomitant formation of the product **177** and alcohol side product **136** in a 4:1 ratio (entry 4, Table 17). Note that in these first four reactions (entries 1–4, Table 17), the presence of the stannane starting material (**176**) in the crude reaction mixture (observed by ^{1}H NMR spectroscopy) showed that stannane homocoupling was not occurring. It was noted that, as in earlier studies (Chapter 2), increasing the time that the stopper was removed to 20 seconds led to incomplete consumption of starting material and homocoupling of the stannane (entry 5, Table 17). Similar results were obtained upon injection into an N_2 backfilled reaction vessel of 1 mL, 2 mL, 5 mL and 10 mL of air using a syringe and an exit needle (entries 6–9, Table 17). It can be seen that as the amount of air injected increases, the amount of product **177** formed in the reaction mixture decreases, with the formation of the alcohol side product **136** approximately constant. It is worth noting that 1 mL of air contains approximately 8.6 μmol O_2 (assuming 21% O_2 in air), which is more than the one equivalent of O_2 per Pd required for oxidation to Pd^{II}, which could either lead to phosphine oxidation and/or promotion of stannane homocoupling.

The injection of 10 mL of dry air, which had been passed through a drying column containing activated 4 Å molecular sieves, led to little change in the outcome (entry 10, Table 17), discounting water as the activating species. Backfilling the headspace above the reaction mixture with atmospheric (entry 11, Table 17) or dry air (entry 12, Table 17), or performing the reaction in an open flask (entry 13, Table 17) led to near-identical results, with no product formation, and partial conversion to the alcohol side-product **136**. Interestingly, whilst all of the previous air-exposed reactions had been black after 24 h, these final three remained yellow (Figure 30(b)).

Table 17 Examination of air volume and temperature effects on an allylic Stille reaction.



Entry	Method of exposure	Ratio[a] 137:177:136	Colour[b]
1	None	89:11:0	yellow
2	None[c]	52:48[d]:0	yellow
3	None[e]	0:100[f]:0	black
4	Stopper removal (5 s)	0:80:20	black
5	Stopper removal (20 s)	13:66:21	black[g]
6	Injection (1 mL)	12:80:10	black[g]
7	Injection (2 mL)	10:79:11	black[g]
8	Injection (5 mL)	27:58:15	black[g]
9	Injection (10 mL)	50:35:15	black[g]
10	Injection (10 mL)[h]	41:40:19	black[g]
11	Backfill	68:0:32	yellow[g]
12	Backfill[h]	68:0:32	yellow[g]
13	Open flask	71:0:29	yellow[g]

[a]As judged by ^{1}H NMR spectroscopy; [b]Colour of reaction mixture after 24 h, see Figure 30(a) for examples; [c]Reaction carried out at 40 °C; [d]*E*:*Z* = 3:1; [e]Reaction carried out at 60 °C; [f]*E*:*Z* = 2:1; [g]Homocoupling of stannane indicated by absence in crude ^{1}H NMR spectrum; [h]Air dried over 4 Å MS before use.

(a)

(b)

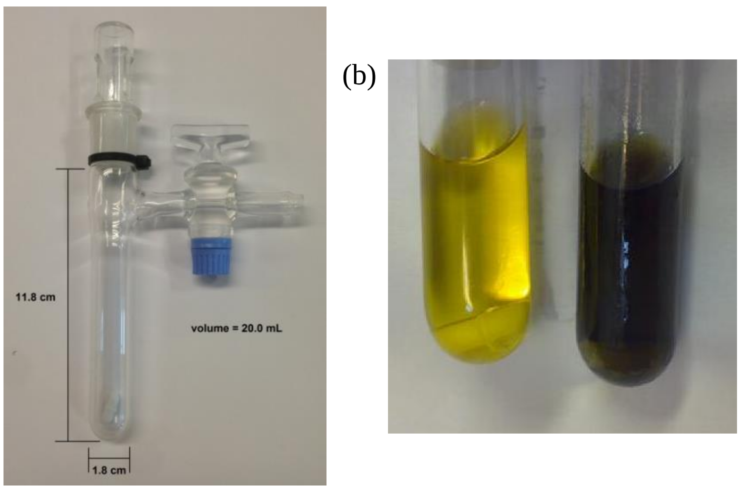
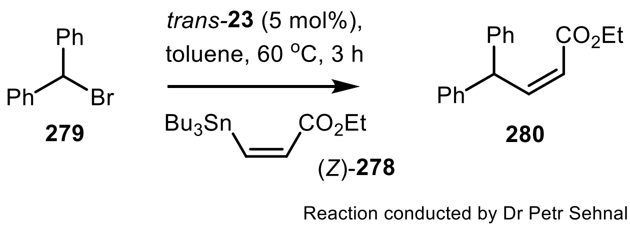


Figure 30 (a) Dimensions of Schlenk tube used for air-exposure studies; (b) Examples of 'yellow' and 'black' reaction mixtures.

It would appear from this preliminary study that although for this system air is required to activate the catalyst at room temperature and achieve efficient catalytic turnover, the presence of too much air supresses the formation of the cross-coupled product, favouring instead the homocoupling of the stannane. The formation of the allylic alcohol **136** appears to be a consistent background reaction when the reaction is exposed to air, constituting 10–20% of the product mixture when the amount of air is limited. The mechanism by which this side-product is formed is unclear, but appears to be independent of the amount of water present in the system.

A positive effect of air has also been observed by other studies in the Fairlamb group, conducted by Dr Petr Sehnal. Upon examination of another model reaction (Scheme 83), it was found that conversion of diphenylbromomethane **279** into product (**280**) only occurred when the reaction was exposed to air. The reaction could be monitored *in situ* using the ReactIR system (with Si probe), which has been shown to be particularly suited to studying cross-coupling reactions.[218-219] No conversion into product was observed when the reagents were stirred with *trans*-**23** at 60 °C for 15 min under an atmosphere of N_2 (Figure 31). At *ca*. 35 min, the reaction mixture was exposed to air for 20 seconds by removal of the stopper (no flow of N_2) before being re-sealed for the remaining reaction time. The reaction rapidly reached completion (within 1 h) and turned a dark brown colour.



Scheme 83 Stille cross-coupling reaction of (*Z*)-**278** and **279** to give **280**.

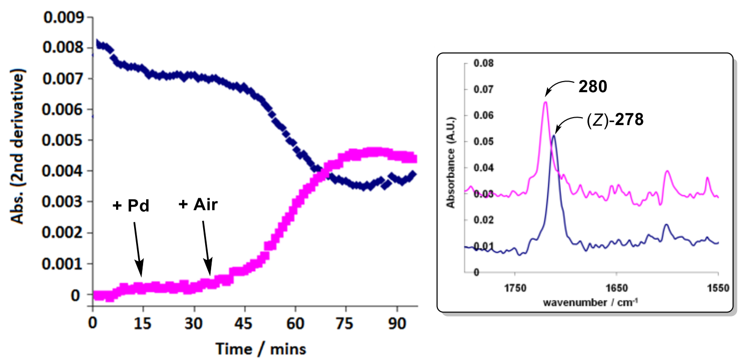
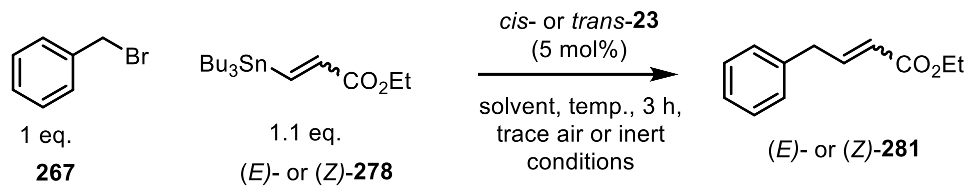


Figure 31 Conversion to product as monitored by ReactIR in reaction in Scheme 83. The conversion is shown as the second derivative which accounts for the gradient changes as a function of peak intensity and allows overlapping peaks to be discerned. Inset: IR spectra for (*Z*)-**278** and **280**. Figure prepared by Prof. I. J. S. Fairlamb.

In many transition-metal-catalysed reactions, a dark brown or black colour may indicate the formation of colloidal metal or metal nanoparticles.[220-221] Therefore the colour change from yellow to black may indicate the presence of Pd nanoparticles (PdNPs) at higher temperatures or in the presence of trace air. A key question is whether the PdNPs are catalytically active or simply a moribund form (*i.e.* a dead-end for catalysis). A more detailed kinetic investigation is required to elucidate the mechanistic intricacies of these reactions and provide proof of a heterogeneous pathway in the presence of trace air.

4.3 Further Investigations

Following this preliminary study, it was thought instructive to study a somewhat simpler system in order to gain a more complete understanding of the processes occurring under different conditions. A simple benchmark reaction was selected (Scheme 84) which was previously reported to work well with catalyst **23**,[54] and five variables were systematically examined: temperature, solvent, catalyst stereochemistry, stannane stereochemistry and exposure to trace air. Reactions were carried out in either toluene or DMF at 60, 70 or 90 °C.



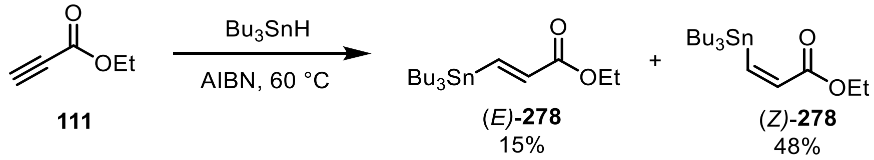
Scheme 84 The benchmark reaction used in the investigations into catalyst **23**.

Reactions were conducted simultaneously with one reaction exposed to 'trace air' and the other kept under an atmosphere of N_2. The exposure to air was carried out in a controlled way using a consistent method:

- All reactions were set up in an identical fashion and on the same scale: benzyl bromide was added to a solution of the stannane and catalyst in the appropriate degassed solvent prepared under an atmosphere of N_2.
- If the reaction was to be exposed to air, the flow of N_2 was closed at the Schlenk side-arm, the stopper was removed for five seconds (timed with a stopwatch), before being replaced and the vessel left sealed for the remainder of the reaction time. The Schlenk tubes used were as depicted in Figure 30(a).
- If the reaction was conducted under 'inert conditions', it was sealed under a flow of N_2 and left sealed for the remainder of the reaction time.

For full experimental details, see general procedure 2 in Chapter 7.

The (*E*)- and (*Z*)-stannanes **278** for use in the screening experiments could be formed in a single reaction by a radical addition of Bu_3SnH to ethyl propiolate (**111**), followed by separation of the isomers by column chromatography on silica gel (Scheme 85).[222]



Scheme 85 Synthesis of (*E*)- and (*Z*)-**278**.

4.3.1 Reactions in Toluene

The reaction was first examined using toluene as a solvent at various temperatures, using both *cis*- and *trans*-**23**, and both the (*E*)- and (*Z*)-stannanes **278**. The results of this are gathered in Figure 32.

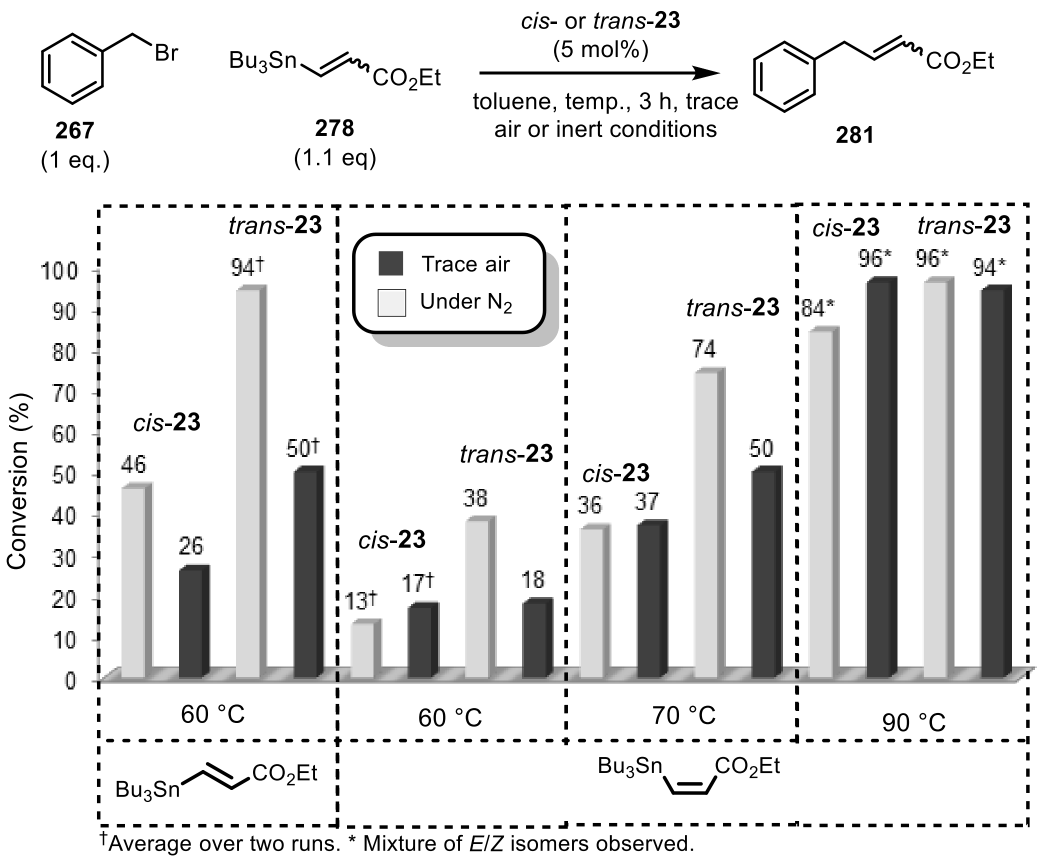
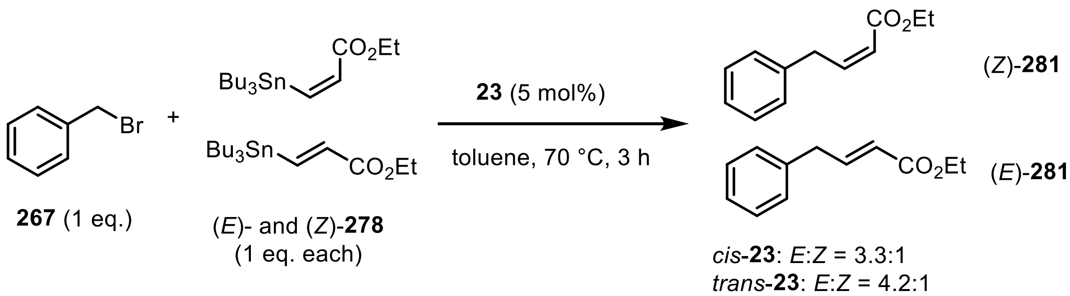


Figure 32 Results of benchmark reaction conducted in toluene at various temperatures. Conversion as judged by ^{1}H NMR spectroscopy. For tabulated data see Appendix 2.

It can be seen from Figure 32 that the reaction is sensitive to temperature. An increase in the reaction temperature from 60 to 70 °C leads to a doubling of conversion, and a further increase to 90 °C affords near-quantitative conversion. At the higher temperatures, partial isomerisation of the stannane was observed, and it was noted that this was exacerbated by trace air. The *trans*-catalyst is more efficient than the *cis*-catalyst in almost every case, and this is likely due to its greater solubility in toluene. The 99% conversion of the reaction previously reported in the literature[50] (*cis*-**23**, (*E*)-**278**, 60 °C, no air) could not be emulated, and this was also attributed to the poor solubility of the catalyst in toluene (incomplete dissolution was observed). The presence of trace air appears to be detrimental to the conversion of the reaction, and this effect is more pronounced at lower temperatures. It was notable that when reactions were exposed to air, they invariably turned black after the 3 h reaction time. In cases where the reaction was conducted under entirely inert conditions, the reaction mixture always remained yellow (the colour of the catalyst in solution). This suggests that air is having a detrimental effect on the activity of the catalyst in this solvent.

It was also noted that (*E*)-**278** reacted faster than (*Z*)-**278**, and in order to confirm this, a competition reaction between the stannanes was carried out, whereby one equivalent of benzyl bromide was allowed to react with one equivalent of each stannane (Scheme 86). The results confirm that benzyl bromide **267** reacts faster with the (*E*)-**278** under catalysis by both *cis*- and *trans*-**23**. The remainder of the excess vinyl stannane was converted to the homocoupled product both reactions.



Scheme 86 Competition experiment between (*E*)- and (*Z*)-**278**.

4.3.2 Reactions in DMF

In order to provide a comparison with the results of the reactions in toluene, the screening of conditions was repeated using DMF as the solvent. DMF is a widely used solvent for many Pd-catalysed cross-coupling reactions, but particularly for the Stille reaction. The benchmark reactions were repeated in DMF and the results are summarised in Figure 33.

It can be seen immediately from the results that the reaction is more efficient in DMF than in toluene. Indeed the reaction using (*E*)-**278** is so efficient that the conversion is essentially quantitative under all conditions screened and no trend can be discerned. The same is true when (*Z*)-**278** is employed at 90 °C. This could be due to the greater solubility of both catalysts in DMF but could also imply that a more active role is being played by the solvent (*e.g.* in stabilisation of the Pd centre). In a similar manner to the toluene reactions, exposure of the reaction mixture to air led to the formation of a black colour, whilst under inert conditions the reaction mixture remained yellow. Using (*Z*)-**278** at 60 °C it appears that trace air has a beneficial effect on the reaction, increasing the conversion by around 20% with both catalysts. Interestingly, this stands in contrast to the reaction conducted in toluene, where the conversion was reduced by exposure to air in a number of instances. At ambient temperature *trans*-**23**, whilst soluble in DMF, fails to afford any product either with or without air, in contrast to the system examined in the preliminary studies.

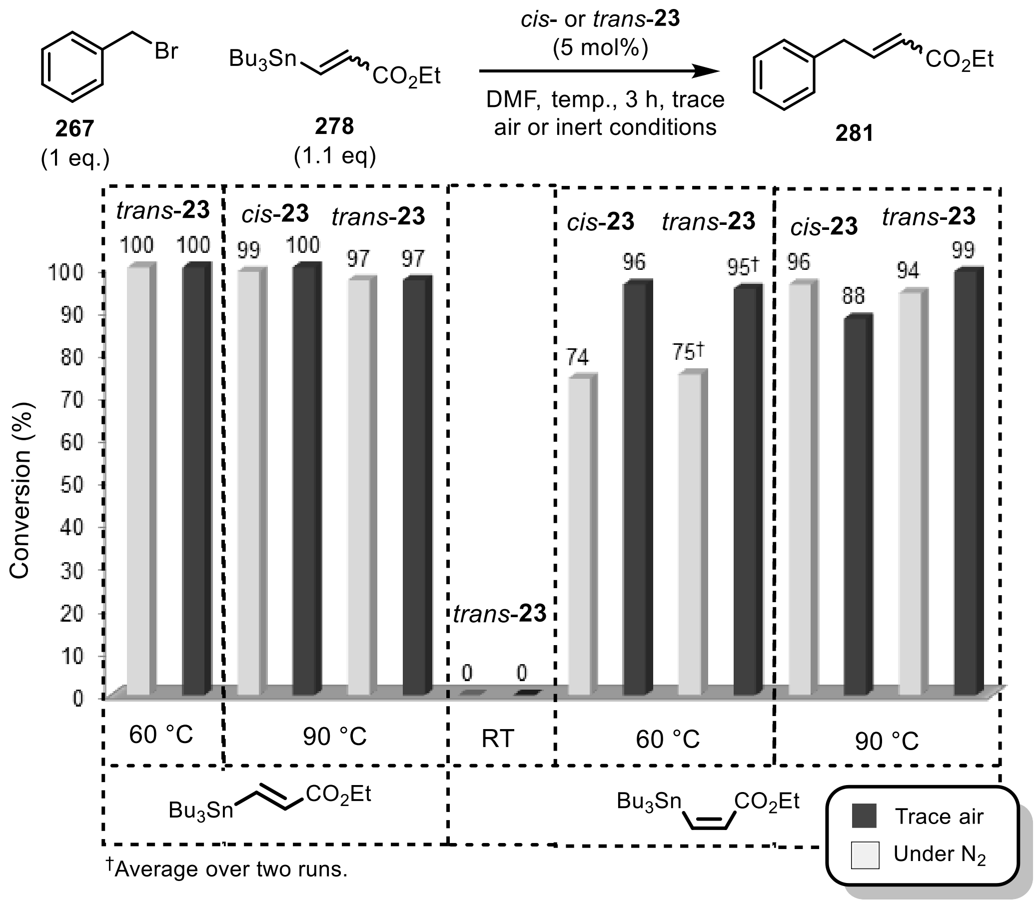
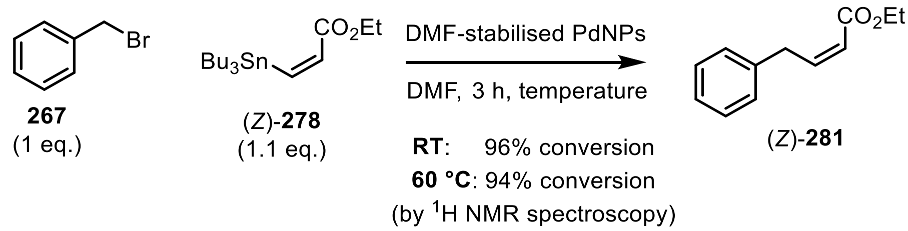


Figure 33 Results of benchmark reaction conducted in DMF at various temperatures. Conversion as judged by ^{1}H NMR spectroscopy. For tabulated data see Appendix 2.

In order to further explore the theory that DMF was beneficial for the catalysis, DMF-stabilised Pd nanoparticles (DMF-PdNPs) reported by Obora[223] were pre-synthesised. It was hypothesised that the DMF-PdNPs ought to be similar to the PdNPs generated from *trans*-**23** in DMF. Interestingly, in order to prepare the DMF-PdNPs, it was found necessary to make modifications to the original procedure:[223] the synthesis only worked when it was carried out in the presence of air; performing the reaction under inert conditions led to the formation of Pd black (see Chapter 7 for experimental details). They were subsequently characterised using XAS methods (see Section 4.1.1.2). When these pre-synthesised nanoparticles were employed in the reaction with (*Z*)-**278** (Scheme 87), the conversion was essentially quantitative under inert conditions, both at room temperature and 60 °C. This outcome is consistent with the hypothesis that similar nanoparticles are forming under our reaction conditions, and that this could be expedited by the presence of trace air.



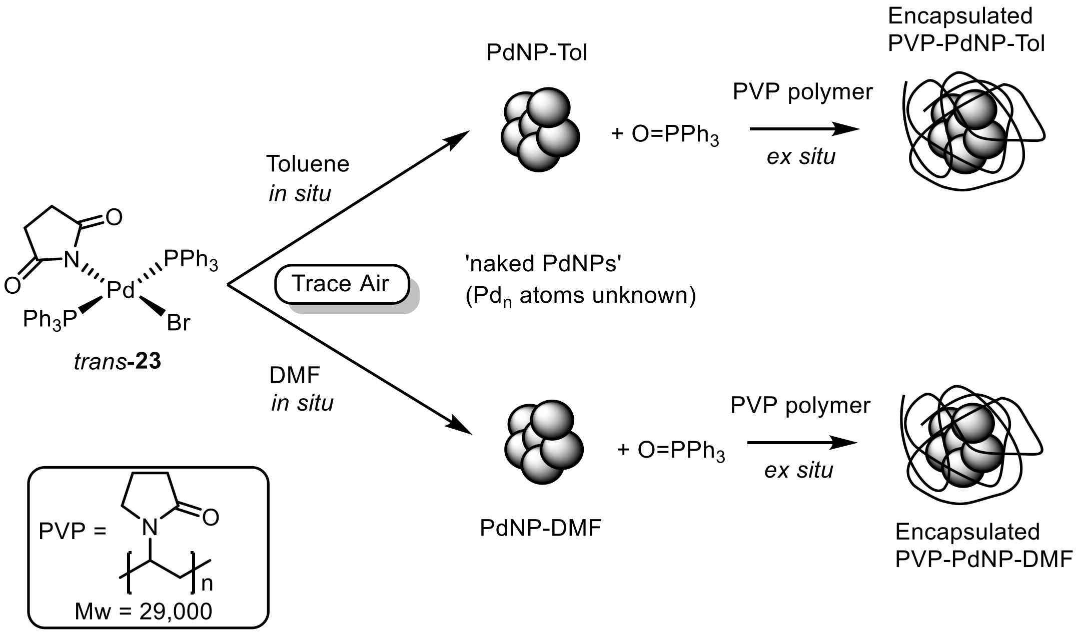
Scheme 87 Benchmark reaction with DMF-stabilised PdNPs.

4.4 Characterisation of the Active Catalytic Species

4.4.1 Air-Exposed Reactions

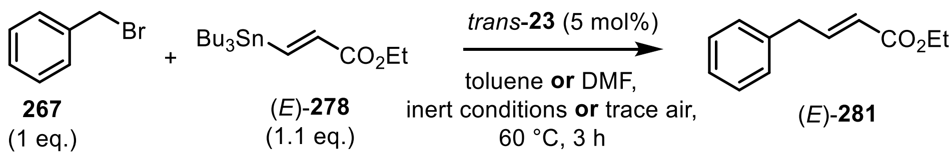
4.4.1.1 Transmission Electron Microscopy Analysis

If PdNPs were indeed forming from complex **23** under our reaction conditions, it would be informative to characterise these particles by transmission electron microscopy (TEM), a technique routinely used to examine samples containing metal particles.[220] This involves passing a beam of electrons through the sample; dense objects scatter the electrons such that an image can be generated of the sample. The instrument used in this study has a resolution of *ca*. 1 nm. As an *ex situ* technique, any particles to be characterised need to be preserved such that they can be removed from the reaction mixture and analysed without changing or aggregating. Therefore a reaction was conducted in each of DMF and toluene, and after 3 h an aliquot was removed from each, ten equivalents (w.r.t Pd) of (poly)vinylpyrrolidinone (Mw = 29,000) were added to encapsulate any nanoparticles present, and the solvent was removed under vacuum. This process is summarised in Scheme 88 (see Chapter 7 for full details).



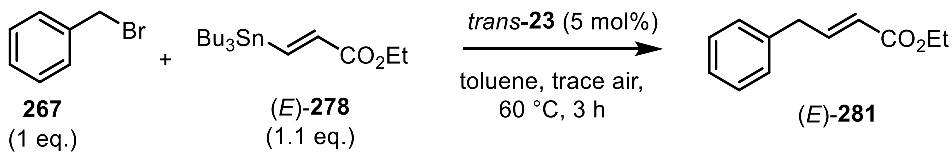
Scheme 88 Encapsulation of *in situ* formed Pd nanoparticles from *trans*-**23**. O=PPh$_3$ was observed by ^{31}P NMR (see Section 4.4.2.1).

Once the particles had been treated in this way, they could be analysed by TEM. This process was carried out for a series of four reactions at 60 °C: in DMF or toluene and with or without exposure to trace air. These reactions are depicted in Scheme 89.



Scheme 89 Reactions used to analyse Pd species present by TEM.

In both reactions which were not exposed to air, no nanoparticles were observed by TEM. However, PdNPs were observed in both samples taken from the air-exposed reactions, and the images captured of the reaction mixtures, along with a histogram analysis of the particle sizes, are shown in Figure 34 and Figure 35.



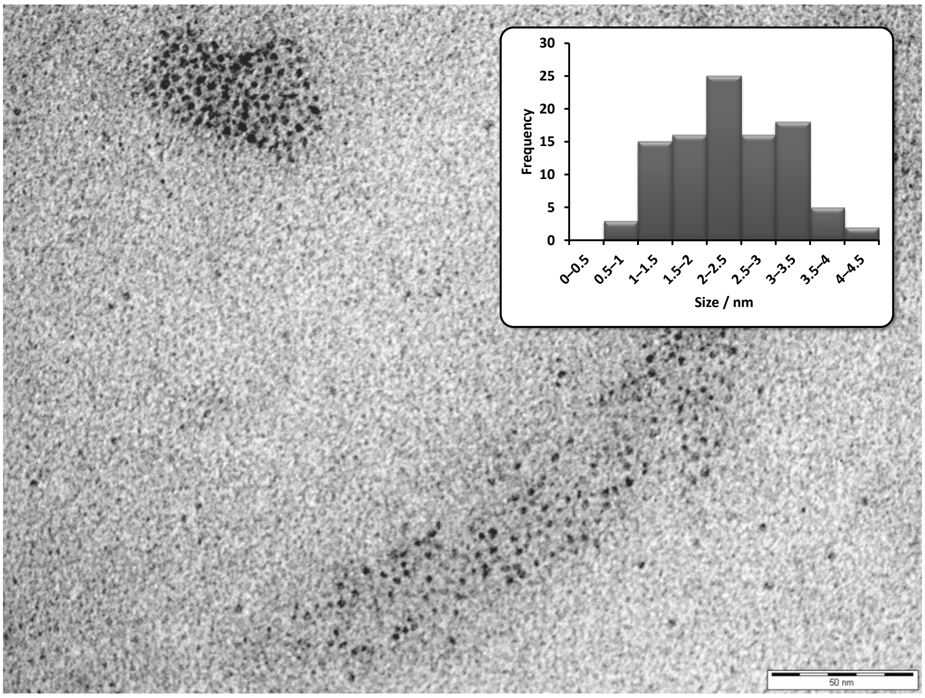


Figure 34 Electron micrograph of reaction mixture (see above scheme) in toluene after 3 h, stabilised by addition of PVP (10 eq. per Pd, Mw = 29,000) before removal of solvent. Inset: histogram of particle diameter (nm) across a sample of nanoparticles (*n* = 100).

Both reactions clearly show the formation of well-defined spherical Pd nanoparticles (most likely truncated icosahedra with (111) surfaces),[224] but there are interesting differences between the nanoparticles formed in different reaction media. The particles from the reaction in toluene show a greater range of sizes and a wider distribution with similar numbers of particles between 1 and 3.5 nm. The particles formed in DMF show a tighter distribution, with a clear modal diameter of 1.5–2 nm. Smaller nanoparticles can in some cases be more active, although other factors such as morpology are also important, and this might explain the greater efficiency of the catalyst in DMF over toluene.[225] These results point to a stabilising effect of DMF on the nanoparticles, leading to less aggregation and so smaller and more active nanoparticles. This goes some way to explaining the different effect of air on the reactions in DMF and toluene.

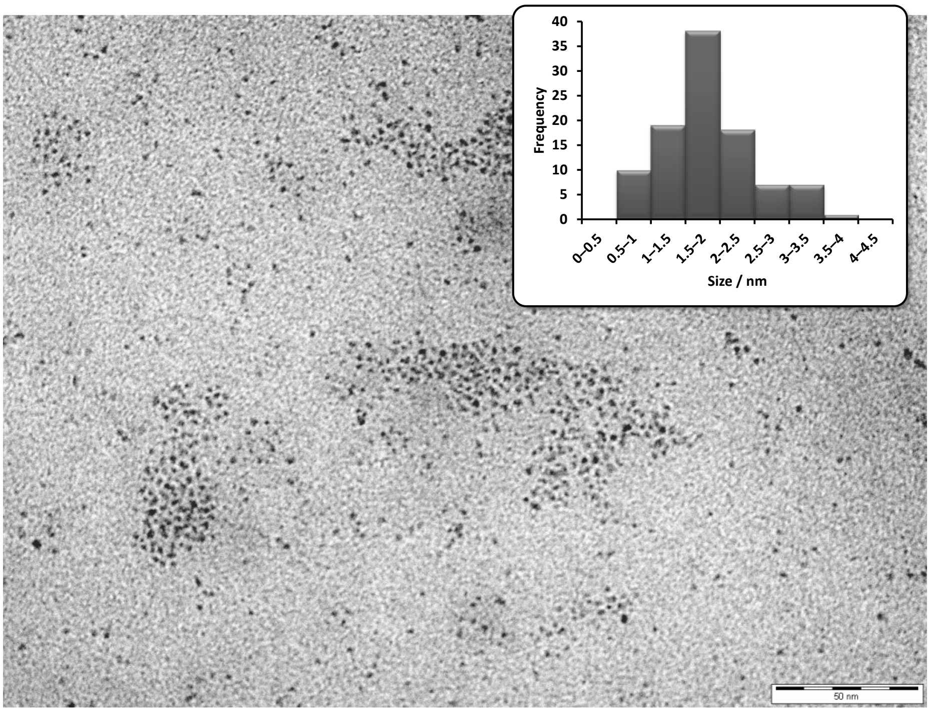


Figure 35 Electron micrograph of reaction mixture (see above scheme) in DMF after 3 h, stabilised by addition of PVP (10 eq. per Pd, Mw = 29,000) before removal of solvent. Inset: histogram of particle diameter (nm) across a sample of nanoparticles (*n* = 100).

TEM analysis was also attempted on the preformed DMF-stabilised nanoparticles employed in the reaction in Scheme 87, but the nanoparticles observed were too small to carry out a meaningful analysis given the maximum resolution of the electron microscope (<1 nm). In the original paper, the TEM analysis showed weak particles of approximately 1.5 nm in size.[223]

4.4.1.2 X-Ray Absorption Spectroscopy Analysis

The PdNPs were further characterised by X-ray absorption spectroscopy (XAS). This technique involves bombarding the sample with X-rays, and detecting the energies of any emitted electrons from the atom of interest (*e.g.* Pd). It allows the structure determination of higher order species such as nanoparticles *in situ* whilst ignoring organic species such as ligands, substrates, additives and solvent. XAS can be split into two techniques from which both electronic and structural information can be gathered: (a) X-ray absorption near edge spectroscopy (XANES) from the absorption edge region, which gives information about the oxidation state and electronic structure of atoms; (b) extended X-ray absorption fine structure spectroscopy (EXAFS) from the scattering pattern, which gives information about the surrounding environment (*e.g.* Pd–Pd, Pd–P and Pd–X interactions can be readily characterised). This technique has been used previously for the characterisation of transition metal NPs under working conditions.[224, 226] All XAS measurements in this study were carried out on Beamline 18 at the Diamond Synchotron, Oxfordshire, by Professors Ian Fairlamb and Adam Lee (Aston University), and Dr Christopher Partlett (Aston University).

The pre-synthesised DMF-stabilised PdNPs reported by Obora[223] were first examined using this technique. A colloidal suspension in DMF (1 mM) was analysed directly at room temperature using the X-ray beam. This experiment confirmed that the PdNPs consist of a mixture of Pd^0 and Pd^{II} sites in a 27:73 ratio (Figure 36). Qualitatively, the EXAFS data shows that the NPs contain a large number of Pd^{II} sites at the surface, an observation consistent with the experimental finding that air was required for the successful synthesis of the NPs.

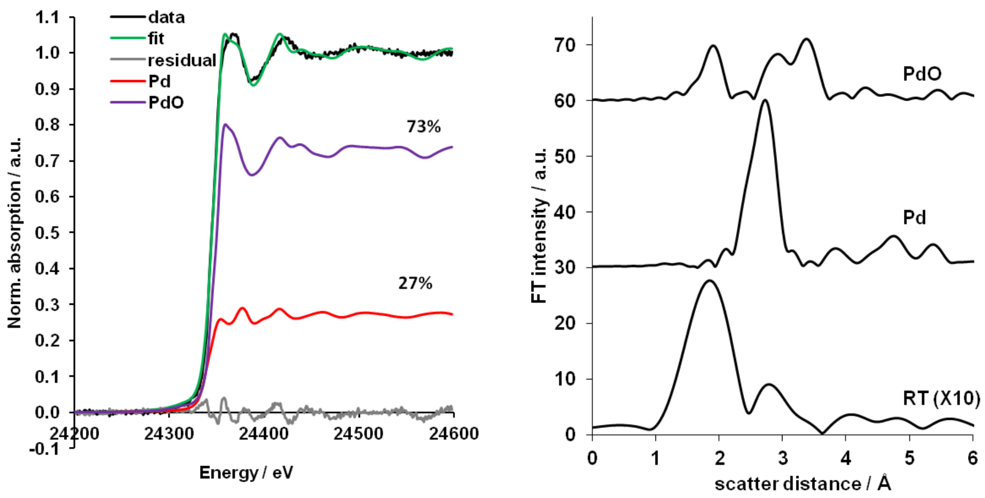


Figure 36 XAS data for the DMF-stabilised PdNPs. Left: XAS data, including the XANES region (below 24.35 KeV) and the EXAFS region (above 24.35 KeV). Right: EXAFS spectrum for the DMF-PdNPs (RT) and appropriate reference spectra (Pd and PdO). Figures prepared by Prof. I. J. S. Fairlamb and Dr C. Partlett (Aston).

An examination of the species arising from the degradation of *trans*-**23** was also carried out by XAS. A DMF solution of the complex was heated to 140 °C in the presence and absence of air; differences in the size, shape and stirring of the in-line reaction vessel to those used in previous studies meant degradation was slow and a higher temperature was required. The EXAFS data (Figure 37) shows that the resulting material consists mainly of Pd^{II} sites, as seen for the DMF-stabilised PdNPs (Figure 36). Additional experiments are required for a more detailed analysis of this data, which is ongoing within the group in collaboration with the team at Aston University.

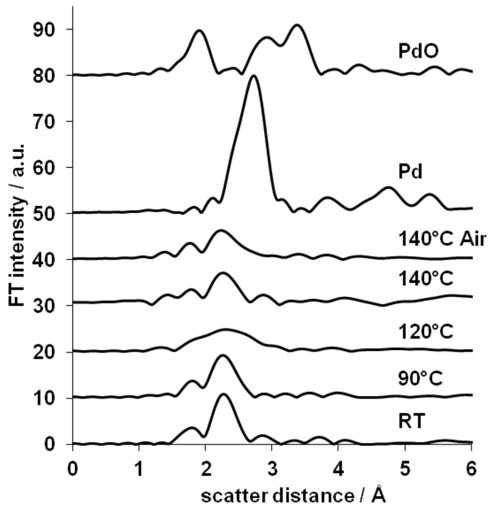
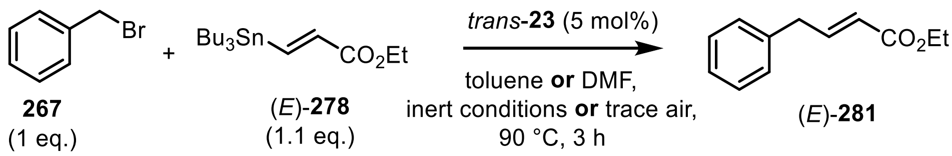


Figure 37 EXAFS data showing the degradation of complex *trans*-**23** with heating. New peaks are noted on the left side of the spectra as the material is heated and exposed to air, more like PdO, showing that there are increasing Pd^{II} sites as part of a more ordered structure. Figure prepared by Prof. I. J. S. Fairlamb and Dr C. Partlett (Aston).

4.4.2 Air-Free Reactions

4.4.2.1 ^{31}P NMR Spectroscopic Analysis

In an attempt to further characterise the Pd species forming under the working reaction conditions, an analysis of the reaction mixtures by ^{31}P NMR spectroscopy was carried out. This involved running the reactions as normal before removing the solvent *in vacuo* and analysing the crude residue by ^{31}P and ^{1}H NMR spectroscopy.



Scheme 90 Reactions used to analyse Pd species present by ^{31}P NMR and LIFDI.

In reactions which were run in the presence of trace air, in both toluene and DMF, only one major peak was present in the ^{31}P NMR spectrum, at δ 29.8 (c and e, Figure 38), and this was attributed to triphenylphosphine oxide (lit.[227] δ 29.5). This suggests that the air in the reaction mixture could be oxidising the phosphine meaning that it binds more weakly to the Pd centre, thereby encouraging the formation of nanoparticles, and could explain the black colour formed when the reaction is exposed to air. In the reaction in toluene which was not exposed to air, a single peak was observed in the ^{31}P NMR spectrum at δ 23.0 (d, Figure 38) which is attributed to the catalyst *trans*-**23** itself (δ 23.0, a, Figure 38) and this suggests that the catalyst is not degrading under the reaction conditions in the absence of air and therefore acting in a homogenous, molecular fashion. In the air-free reaction in DMF, two new signals were observed at δ 23.8 and δ 22.6 (b, Figure 38). These did not match the reference compound $PdBr_2(PPh_3)_2$, which gave a signal at δ 26.6 (f, Figure 38), nor the signal which appeared (amongst others) at δ 32.3 when one equivalent each of PPh_3 and NBS were combined in $CDCl_3$ solution (g, Figure 38).[228-229]

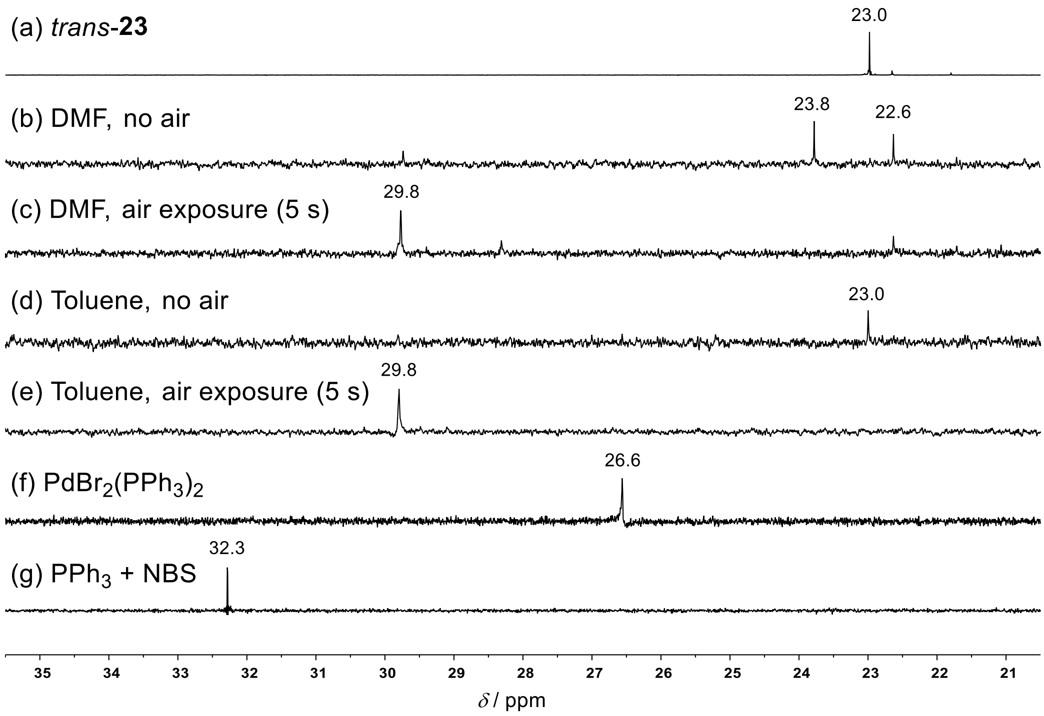


Figure 38 ^{31}P NMR spectra (167 MHz, $CDCl_3$) of crude reaction mixtures conducted under various conditions along with reference spectra.

4.4.2.2 LIFDI Mass Spectrometry Analysis

Liquid Injection Field Desorption Ionisation (LIFDI) mass spectrometry is a useful technique for analysing catalytic intermediates as it minimises fragmentation and so allows the observation of fragile species.[230] Samples were taken of the air-free reactions (Scheme 90) at the end of the reaction and after removal of solvent. When these samples were analysed by LIFDI-MS, a number of new peaks were observed, none of which occurred at m/z = 809, corresponding to the molecular ion of *trans*-**23**. In the air-free toluene reaction, the base peak occurred at m/z = 623 and could not be assigned, although the isotope pattern suggested that it contained Pd. However, a peak was also observed at m/z = 901, the isotope pattern of which closely matches that of a chemical formula of $C_{48}H_{44}O_2P_2PdBr$ (Figure 4.5). This species was also present as a minor component in the air-free DMF reaction, and has been assigned to species **I** (Figure 39). This ion can be envisaged to arise by the loss of a succinimide or bromide anion from a suspected Pd^{IV} intermediate (species **III**, where X = anionic or carbon-centred ligand). In DMF, the base peak occurred at m/z = 645, and this satisfies the chemical formula $C_{26}H_{23}N_2O_4PPdBr$ and closely matches the theoretical isotope pattern shown below. This peak has been assigned the structure (species **II**) shown in Figure 39 and possibly derived from a species such as **IV**.

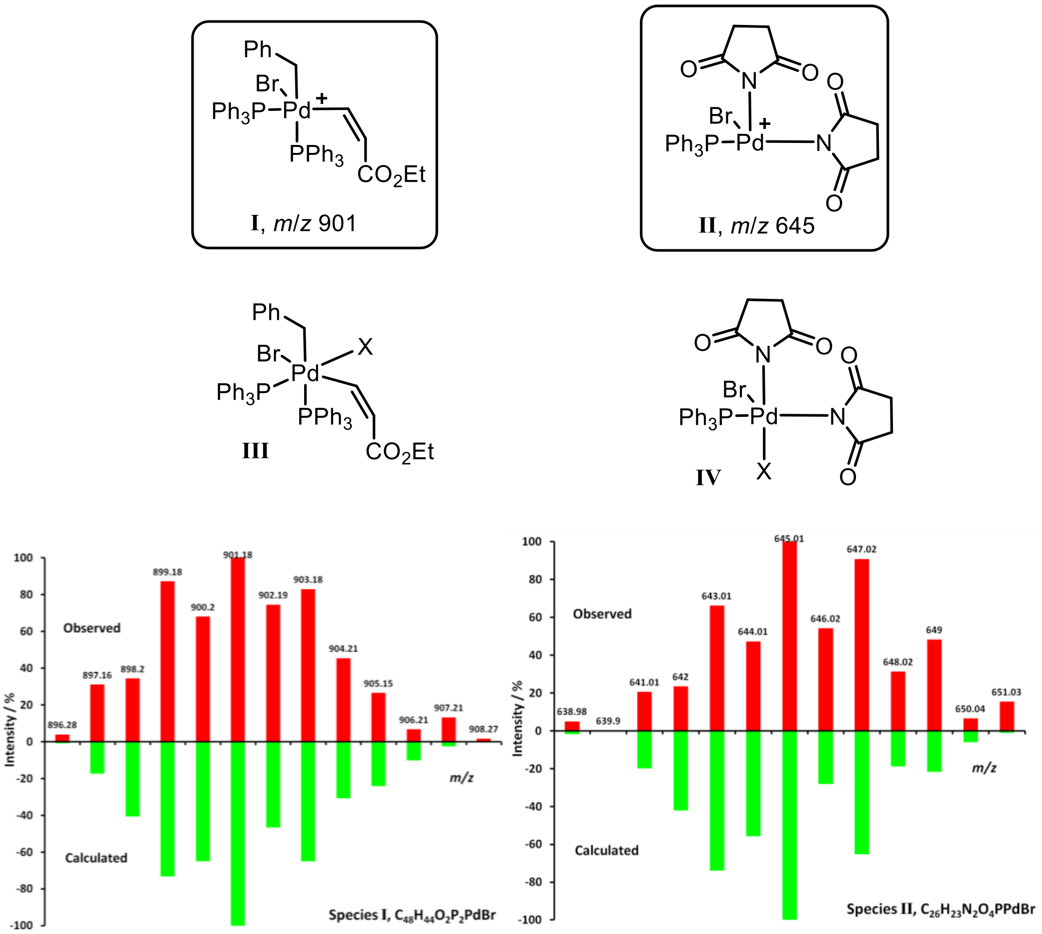


Figure 39 Measured and theoretical isotope patterns and proposed structures for species **I** and **II**, observed in reaction mixtures (Scheme 90) in toluene and DMF. Figures prepared by Prof. I. J. S. Fairlamb.

These results suggest that Pd^{IV} intermediates are present when the reaction is run in the absence of air. Further studies are necessary to assess whether the concentration of the species detected by LIFDI-MS change over time (*i.e.* during catalytic turnover).

4.5 Summary

Based on the observations described above, it is suggested that two catalytic pathways are operative, depending on the reaction conditions. When a trace of air is present, catalytically active Pd nanoparticles are rapidly formed, and these are more catalytically efficient in DMF than in toluene (potentially due to stabilisation by DMF solvent). These nanoparticles have been observed by TEM and those in DMF shown by EXAFS to consist of a mixture of Pd^0 and Pd^{II}. Triphenylphosphine oxide has also been observed in the air-exposed reactions, suggesting that phosphine oxidation may play a role in nanoparticle formation in these cases. In the absence of air, the catalysis proceeds in a homogenous fashion, possibly *via* a $Pd^{II/IV}$ manifold. New species, potentially derived from Pd^{IV} intermediates, have been observed by ^{31}P NMR spectroscopy and LIFDI-MS.

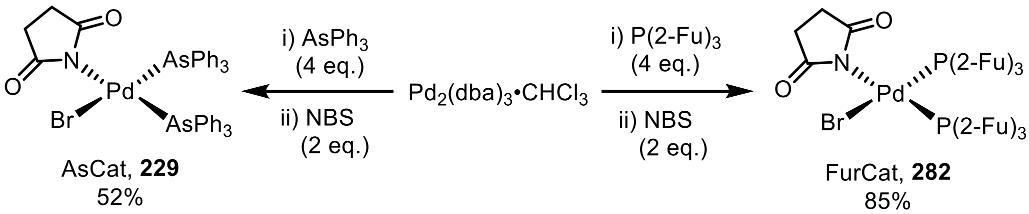
Chapter 5: AsCat and FurCat

5.1 $AsPh_3$ and $P(2\text{-}Fu)_3$ Ligands in Palladium Catalysis

Farina and Krishnan have reported that, in both polar and non-polar solvents, the rate of the Stille cross-coupling reaction can be heavily dependent on the ligands used with Pd.[172, 231] They found that the rate of reaction can be dramatically increased by employing more weakly coordinating ligands such as $AsPh_3$ or $P(2\text{-}Fu)_3$, in preference to PPh_3, in combination with the Pd^0 precursor complex Pd_2dba_3, allowing reactions to be run at a lower temperature. This has since become a widely used catalyst system for the Stille reaction, and whilst well-defined complexes such as $Pd(AsPh_3)_4$,[232] $PdCl_2(AsPh_3)_2$[233] and $PdCl_2(P(2\text{-}Fu)_3)_2$[234] have been prepared and described, complexes containing these ligands have found only occasional use in catalysis, despite their potential. Inspired by the success of the PPh_3-containing complex $PdBr(N\text{-}succ)(PPh_3)_2$ **23**, it was hoped to combine the rate enhancement afforded by these ligands with the efficiency and selectivity of succinimide-based catalysts, and the synthesis of two novel catalysts encompassing $AsPh_3$ and $P(2\text{-}Fu)_3$ ligands was undertaken.

5.2 Catalyst Synthesis and Characterisation

Both complexes, $PdBr(N\text{-}succ)(AsPh_3)_2$ (**229**, 'AsCat') and $PdBr(N\text{-}succ)(P(2\text{-}Fu)_3)_2$ (**282**, 'FurCat'), were successfully synthesised by adapting the same procedure used to synthesise *cis*-**23** (Scheme 91).



Scheme 91 Synthesis of complexes AsCat (**229**) and FurCat (**282**).

Both complexes were isolated as pale brown air- and moisture-stable solids in moderate to good yields. Complex **229** appeared in the ^1H NMR spectrum in an approximately 4:1 *cis*:*trans* ratio. It appeared to be unstable in solution, isomerising entirely to the *trans* isomer over 24 h at RT in $CDCl_3$ or CD_2Cl_2 with gradual decomposition (indicated by a relative increase in the intensity of the peak corresponding to free NBS) and formation of Pd black. The use of dry $CDCl_3$ and preparation of the NMR sample in a glovebox did not affect the rate of decomposition, suggesting that it is not water- or acid-mediated. Both the isomerisation and decomposition were much more rapid in C_6D_6 and acetone-d_6.

Complex **282** behaved similarly, with its ^{1}H and ^{31}P NMR spectra in CD_2Cl_2 indicating an approximately 9:1 *cis*:*trans* ratio. Isomerisation and decomposition were appreciably slower than for the $AsPh_3$-based catalyst, with the isomeric ratio reaching 1:1 after 24 h at RT in solution with partial decomposition.

It is interesting to compare these observations to the much greater stability observed of complex *cis*-**23** in CD_2Cl_2 or $CDCl_3$ solution at room temperature, and these results reflect the expected properties of the catalysts in solution: the $AsPh_3$ ligand should dissociate much more readily than the $P(2\text{-Fu})_3$ which in turn should be more labile than PPh_3.

A single crystal X-ray diffraction structure of *trans*-**229** was obtained (Figure 40), with the crystals grown by vapour diffusion of pentane into a saturated solution of the complex in CH_2Cl_2. For full details see Appendix 3.

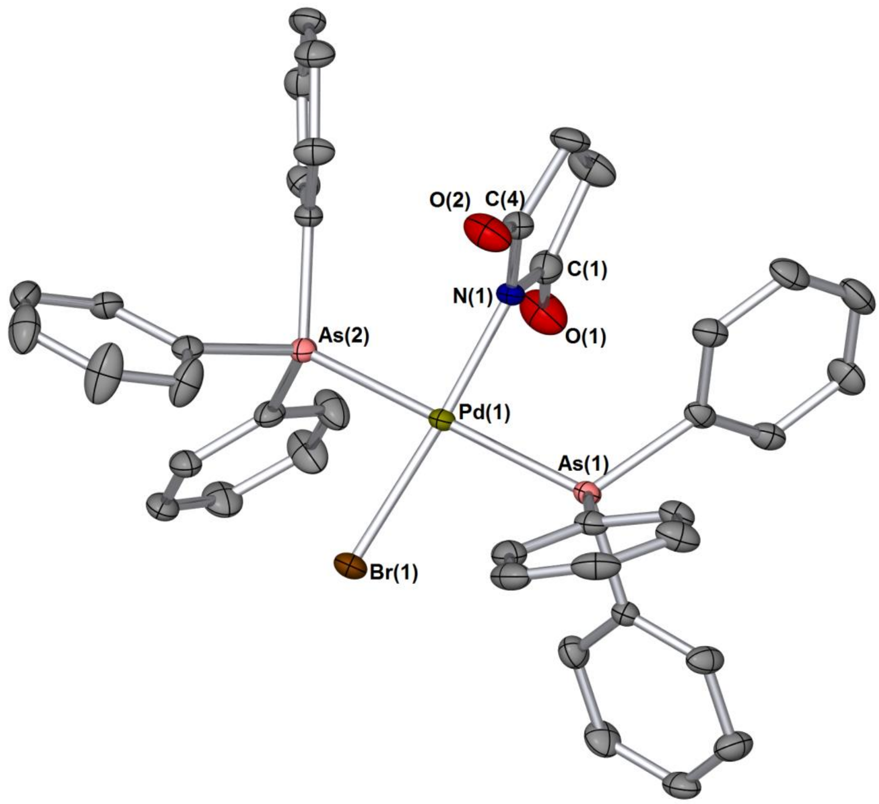
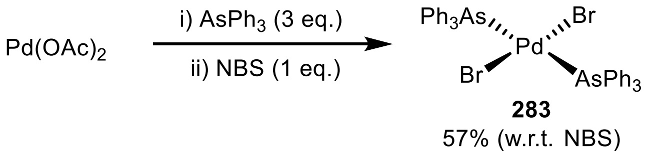


Figure 40 Single crystal X-ray diffraction structure of complex **229**. Hydrogen atoms removed for clarity. Thermal ellipsoids shown with probability of 50%. Selected bond lengths (Å): Pd(1)–As(1): 2.4229(4), Pd(1)–Br(1): 2.4338(4), Pd(1)–As(2): 2.3914(4), Pd(1)–N(1): 2.025(2). Selected bond angles (°): N(1)–Pd(1)–As(1): 90.69(7), As(1)–Pd(1)–Br(1): 92.969(13), Br(1)–Pd(1)–As(2): 87.471(13).

An attempt to synthesise compound **229** using the cheaper and more readily available precursor $Pd(OAc)_2$ led to only small amounts of impure product being isolated, the main side product being *trans*-$PdBr_2(AsPh_3)_2$, which was isolated in 57% yield (w.r.t. NBS) as a bright yellow solid.



Scheme 92 Attempted synthesis of **229** from $Pd(OAc)_2$, resulting in the formation of **283**.

Interestingly, this simple compound has received very limited attention in the literature, with only sporadic reports and incomplete characterisation data available.[235-236] The *trans* stereochemistry was confirmed by single crystal X-ray diffraction (Figure 41), with the crystals grown by slow evaporation from $CHCl_3$. For full details see Appendix 3.

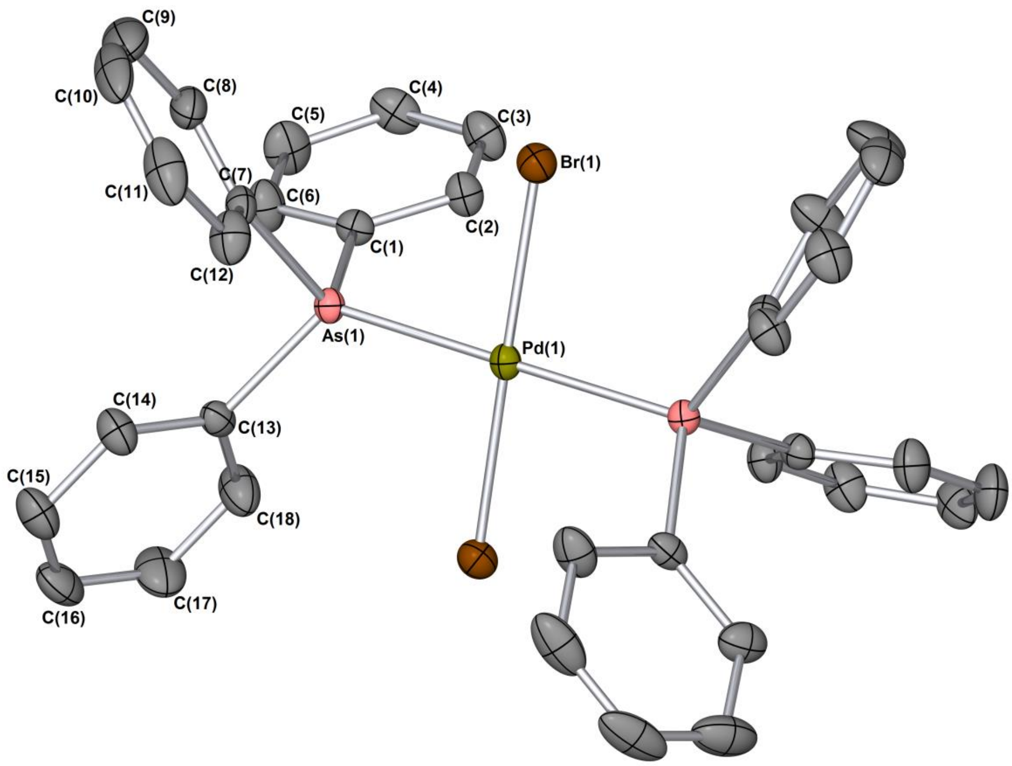
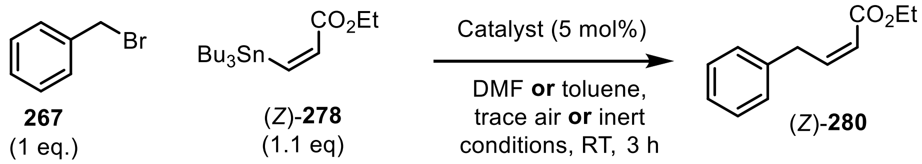


Figure 41 Single crystal X-ray diffraction structure of complex **283**. Hydrogen atoms and co-crystallised $CHCl_3$ removed for clarity. Thermal ellipsoids shown with probability of 50%. Selected bond lengths (Å): Pd(1)–As(1): 2.4043(3), Pd(1)–Br(1): 2.4180(3).

5.3 Preliminary Testing

As a preliminary test, the catalysts' activities were evaluated in the benchmark reaction explored previously (see Chapter 4) at ambient temperature (Table 18).

Table 18 Application of novel catalysts **229** and **282** to benchmark reaction.



Entry	Catalyst	Solvent	Trace air[a]	Conv. / %[b]
1	AsCat (**229**)	DMF	no	89[c]
2	AsCat (**229**)	DMF	yes	84[d]
3	AsCat (**229**)	toluene	no	14
4	AsCat (**229**)	toluene	yes	8
5	FurCat (**282**)	DMF	no	15
6	FurCat (**282**)	DMF	yes	15
7	*trans*-**23**	DMF	no	0
8	*trans*-**23**	DMF	yes	0

[a]Reaction mixture exposed to air for five seconds (see Chapter 4). [b]Conversion judged by ^{1}H NMR spectroscopy. [c]Average over three runs. [d]Average over two runs.

It can be seen that in this reaction in DMF the activity of catalyst **229** is very good at RT, in contrast to that of catalyst **282**, which gives poor conversion, and catalyst *trans*-**23**, which is completely inactive. It is interesting to note the difference in activity for catalyst **229** observed when the solvent is switched from DMF to toluene. This is presumed to be due to catalyst stability: rapid degradation was observed in the similar non-polar solvent C_6D_6. Air seems to have little effect on the activity of either catalyst, and in this system does not activate the PPh_3-based precatalyst *trans*-**23** (see also Chapter 4).

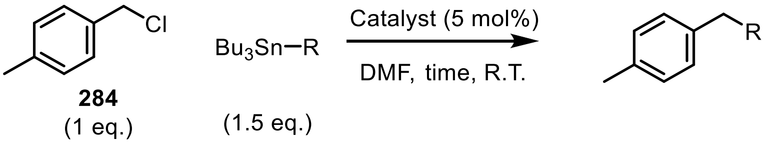
5.4 Benzyl Chloride Stille Couplings

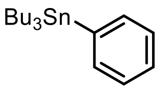
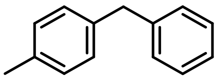
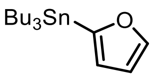
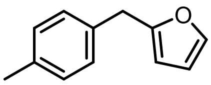
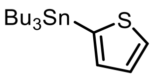
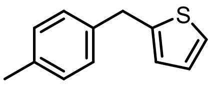
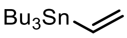
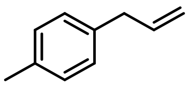
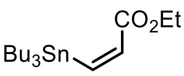
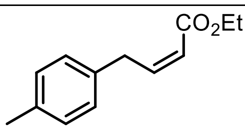
Following these initial studies, attention turned to the Stille coupling of benzyl chlorides. There are only limited reports of Stille couplings with benzyl chlorides,[53, 237-239] and these invariably require an elevated temperature (typically 60–80 °C). As diarylmethane derivatives are currently receiving much attention as bioactive compounds,[240] we proposed that this might be a mild, general and useful method for their synthesis.

5.4.1 Scope of Organostannanes

A screen of coupling reactions using the test substrate 4-methylbenzyl chloride (**284**) and various organostannanes was carried out, using 5 mol% of each catalyst in DMF (Table 19). Gratifyingly it was found that all of the stannanes tested could be coupled with a very high efficiency, and moreover the activities of the catalysts appeared to be complementary.

Table 19 Stille cross couplings of 4-methylbenzyl chloride (**284**) with various stannanes.

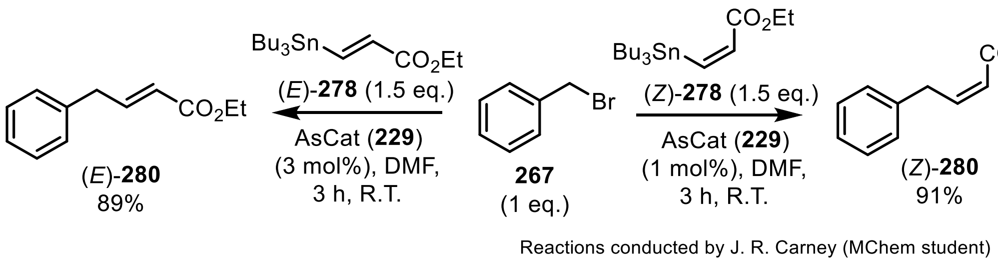


Entry	Stannane	Product	Catalyst	Time / h	Conv.[a, b] / %
1	 **285**	 **286**	AsCat (**229**)	24	>99 (88)
2			AsCat (**229**)	24	99 (83)[c]
3			FurCat (**282**)	24	27
4			*trans*-**23**	24	0
5			$PdBr_2(AsPh_3)_2$ (**283**)	24	>99
6	 **287**	 **288**	AsCat (**229**)	24	54
7			FurCat (**282**)	3	>99 (83)
8	 **289**	 **290**	AsCat (**229**)	24	8
9			FurCat (**282**)	24	>99 (97)
10	 **291**	 **292**	AsCat (**229**)	24	99[d]
11			FurCat (**282**)	24	98[d]
12	 (*Z*)-**278**	 **293**	AsCat (**229**)	24	27
13			AsCat (**229**)	72	87 (83)

[a]Percentages refer to conversion to product as judged by ^{1}H NMR spectroscopy. [b]Numbers in parentheses refer to yields of isolated product following purification on SiO_2–K_2CO_3. [c]Reaction conducted using propylene carbonate solvent. [d]Product not isolated due to volatility.

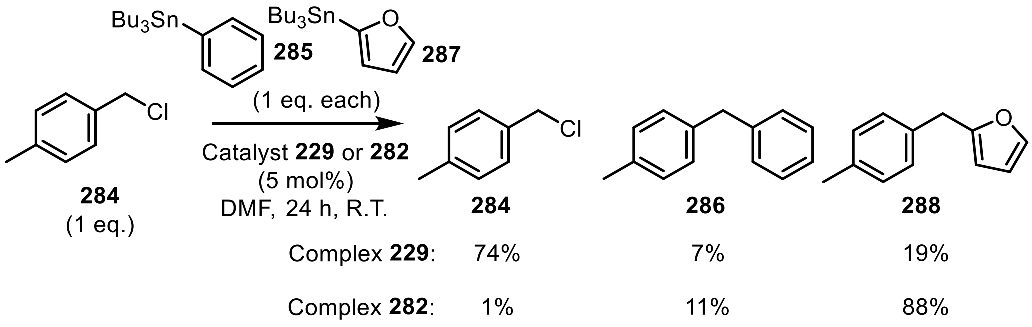
The triphenylarsine-based catalyst **229** is efficient at mediating coupling with tributylphenylstannane **285** in DMF (entry 1, Table 19), and also in propylene carbonate (entry 2, Table 19), a 'green' replacement solvent for DMF which has been successfully employed in a number of Pd-mediated transformations including Heck reactions,[241] direct arylations[242] and allylic substitutions.[243] In contrast, the tri(2-furyl)phosphine-based catalyst **282** gives only modest conversion (entry 3, Table 19), whilst the analogous triphenylphoshine-based succinimide catalyst, Pd(*N*-succ)Br(PPh_3)$_2$ **23**, gives no conversion at room temperature (entry 4, Table 19). Interestingly, the bis-bromide complex $PdBr_2(AsPh_3)_2$ (**283**) also gives complete conversion in this reaction (entry 5, Table 19). Coupling of the electron-rich heteroaromatic stannanes **287** and **289**, based on furan and thiophene respectively, is efficiently mediated by complex **282**, but not by **229** (entries 6–9, Table 19). Both catalysts are efficient with tributylvinylstannane **290** (entries 10 and 11, Table 19). The unreactive stannane (*Z*)**-279** could be coupled using catalyst **229** after extended reaction times (entry 13, Table 19), demonstrating the stability of the catalyst under the reaction conditions, despite the low turnover frequency in this case. Where high conversions were attained, pure products could be readily isolated following a simple aqueous workup and flash chromatography using SiO_2–K_2CO_3 (9:1, *w*/*w*) as the stationary phase in order to remove organotin impurities.[244]

In contrast to the slow reaction of stannane (*Z*)**-278** with a benzyl chloride, the reaction of both (*Z*)**-278** and its isomer (*E*)**-278** were rapid (3 h) with benzyl bromide (**267**), even at lower catalyst loadings, with the products being obtained in high yields in both cases (Scheme 93).



Scheme 93 Coupling of benzyl bromide (**267**) with electron-deficient stannanes (*E*)- and (*Z*)-**278**, mediated by catalyst **229**.

The intriguing complementarity exhibited by the two catalysts could be rationalised by considering the interaction between each catalyst with the stannanes **285** and **287**. The more labile catalyst **229** was rapidly degraded by the more reactive 2-furyl-derived stannane **287**, leading to decomposition of the catalyst, potentially into an inactive form of Pd black, before complete conversion to the product could be attained. In contrast, with the phenyl-derived stannane **285**, the catalyst is stable enough to facilitate full conversion to product without degrading. By comparison, the more stable catalyst **282** is not ‘activated’ with the phenyl stannane (although the nature of this ‘activation’ is not known), leading to sluggish reaction and low conversion. With the more electron-rich stannane **287**, the catalyst enables rapid conversion to the desired product. To test this proposal, a competition reaction was carried out with each catalyst and both stannanes, and the product distribution analysed (Scheme 94).



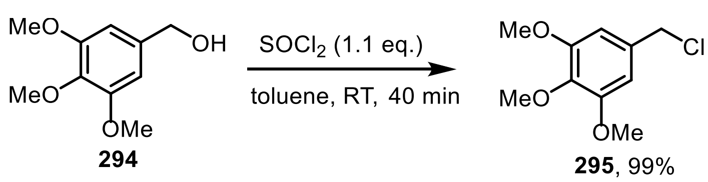
Scheme 94 Competition reactions between stannanes **283** and **285** with each catalyst.

The results seen from these reactions are consistent with the proposal above. With complex **229**, the presence of the furylstannane **287** leads to rapid degradation of the catalyst, and the recovery of large amounts of starting material, although it is interesting to note that more of the furan **288** is formed than the benzyl compound **286**, suggesting that coupling of the furyl stannane is faster. With complex **282**, almost all of the starting material is consumed, and much more of the furan product **288** formed suggesting that the catalyst is stable and that the furylstannane couples faster.

5.4.2 Synthesis of Benzyl Chlorides

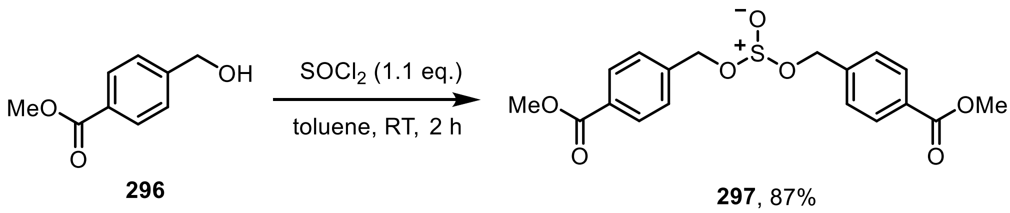
It was important to screen the scope of the reaction with respect to the structure and electronics of the benzyl chloride coupling partner. Whilst many benzyl chlorides are cheap and commercially available, in this case, a number of the substrates were synthesised from various starting materials.

3,4,5-Trimethoxybenzyl chloride **295** was readily available from the corresponding benzyl alcohol by treatment with $SOCl_2$ under literature conditions (Scheme 95).[245]



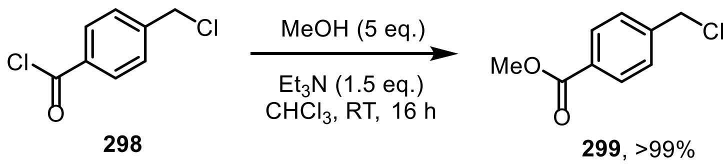
Scheme 95 Synthesis of 3,4,5,-trimethoxybenzyl chloride **295**.

An attempt to use the same procedure on the alcohol methyl 4-(hydroxymethyl)benzoate **296** led to a high yield of the unexpected novel sulfite ester **297** (Scheme 96). Extending the reaction time, or stirring this product with HCl did not lead to the formation of any of the desired benzyl chloride.



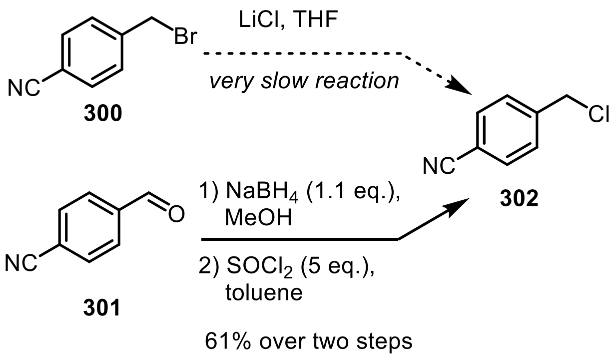
Scheme 96 Unexpected formation of sulfite ester **297**.

The use of an alternative literature method,[246] employing TsCl and DBU also did not afford benzyl chloride, however, the methanolysis of 4-(chloromethyl)benzoyl chloride[247] (**298**) led to smooth conversion to the desired product **299** (Scheme 97).



Scheme 97 Synthesis of methyl 4-(chloromethyl)benzoate **299**.

Attempts to obtain 4-cyanobenzyl chloride (**302**) from the corresponding bromide **300** by reaction with LiCl in THF[248] led to very slow conversion into product, with only 89% conversion achieved after 65 h at reflux (Scheme 98). Since the product was inseparable from the bromide starting material, this was not a practical approach. The target compound could instead be obtained efficiently in two steps from 4-cyanobenzaldehyde (**301**) by reduction[249] followed by treatment with excess $SOCl_2$.

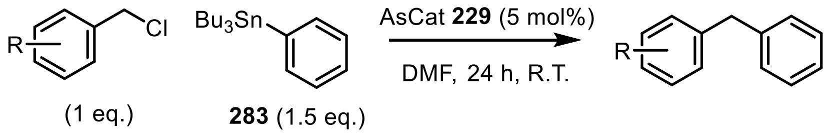


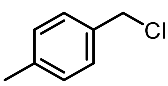
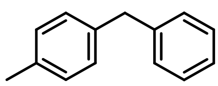
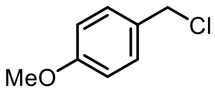
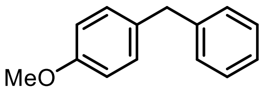
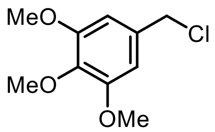
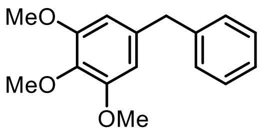
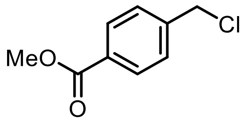
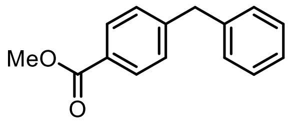
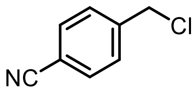
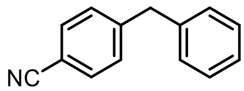
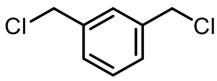
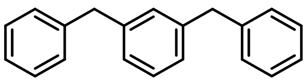
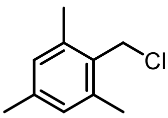
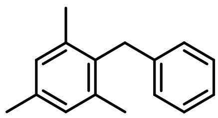
Scheme 98 Synthesis of 4-cyanobenzyl chloride **302**.

5.4.3 Scope of benzyl chlorides

With the required benzyl chlorides in hand, a screen of different coupling partners was carried out under the same conditions used above, first with tributylphenylstannane **285** in combination with catalyst **229** (Table 20).

Table 20 Substrate scope of various benzyl chlorides coupling with tributylphenylstannane **285** using catalyst **229**.



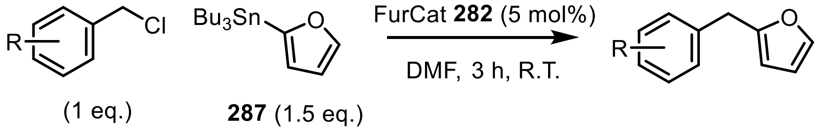
Entry	Benzyl chloride	Product	Yield[a] / %
1	 **284**	 **286**	88
2	 **303**	 **304**	92
3	 **295**	 **305**	83
4	 **299**	 **306**	67
5	 **302**	 **307**	94[b]
6	 **308**	 **309**	79[c]
7	 **310**	 **311**	72

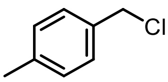
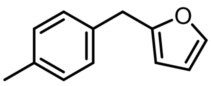
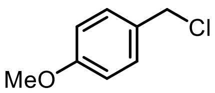
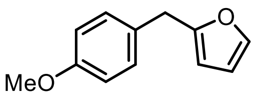
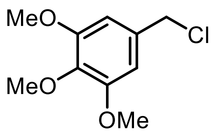
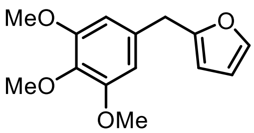
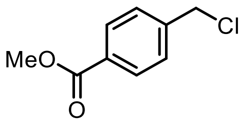
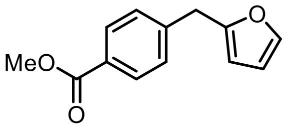
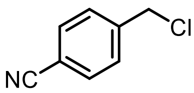
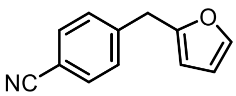
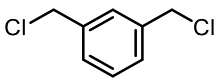
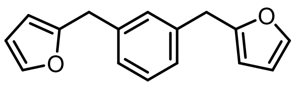
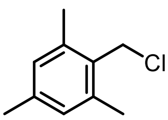
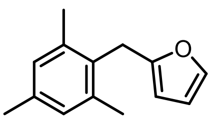
[a]Percentages refer to yields of isolated product following purification on SiO_2–K_2CO_3. [b]Reaction conducted at 40 °C. [c]Reaction carried out with 3 eq. organostannane and 6 mol% catalyst.

Gratifyingly, the catalyst was found to be compatible with a wide range of functionality on the benzyl chloride, including electron rich (entries 2 and 3, Table 20) and electron deficient (entry 4, Table 20) examples, with the cross-coupled products isolated in excellent yields. The very electron deficient 4-cyanobenzyl chloride (**302**) required gentle heating (40 °C) for an efficient reaction (entry 5, Table 20). A double coupling on a *bis*-benzyl chloride **309** was efficient (entry 6, Table 20), and substitution *ortho* to the benzyl position did not affect the reaction (entry 7, Table 20).

The screening was repeated using tributyl(2-furyl)stannane **287** in combination with catalyst **282** (Table 21).

Table 21 Substrate scope of various benzyl chlorides coupling with tributyl(2-furyl)stannane **287** using catalyst **282**.



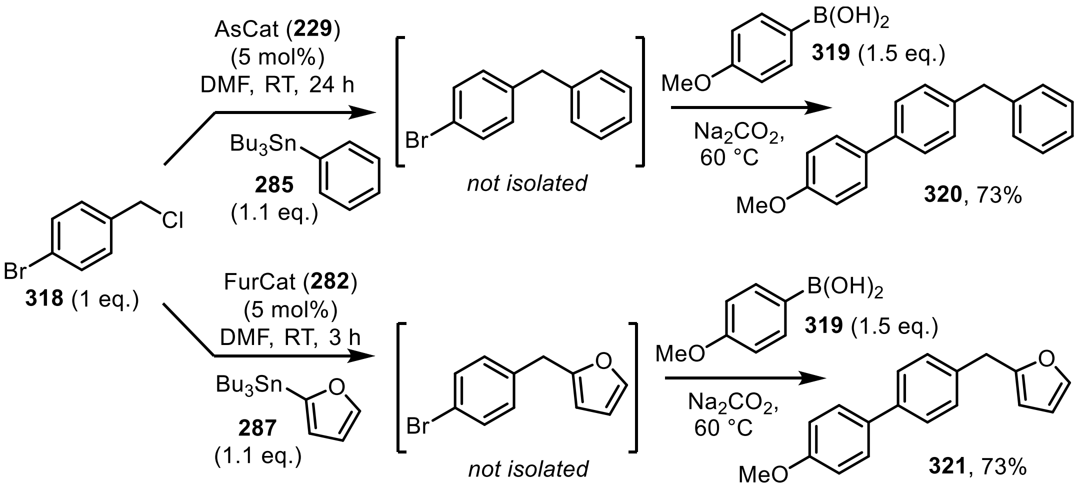
Entry	Benzyl chloride	Product	Yield[a] / %
1	 **284**	 **288**	83
2	 **303**	 **312**	89
3	 **295**	 **313**	77
4	 **299**	 **314**	74
5	 **302**	 **315**	87[b, c]
6	 **308**	 **316**	89[d]
7	 **310**	 **317**	83[c]

[a]Percentages refer to yields of isolated product following purification on SiO_2–K_2CO_3. [b]Reaction conducted at 40 °C. [c]Reaction time 24 h. [d]Reaction carried out with 3 eq. organostannane and 6 mol% catalyst.

As with catalyst **229**, the 2-furylphosphine-derived catalyst **282** was fully compatible with the same array of substitution on the benzyl chloride, with the desired cross-coupling products isolated in comparable yields in all cases. All couplings were complete within 3 h, with the exception of the electron-deficient 4-cyanobenzyl chloride **302** (entry 5, Table 21), which required 24 h at 40 °C, and the doubly *ortho*-substituted trimethyl benzyl chloride **317** (entry 7, Table 21), which required 24 h at RT.

5.4.4 Tandem Stille–Suzuki Reactions

One of the most remarkable aspects of succinimide-containing catalysts is the high selectivity they display for benzyl electrophiles over aryl electrophiles, a feature which has been previously demonstrated with complex **23**.[50] Pleasingly, upon reacting 4-bromobenzyl chloride (**318**) with tributylphenylstannane **285** or tributyl(2-furyl)stannane **287**, using complex **229** or **282** respectively, smooth conversion was observed to the product resulting from reaction exclusively at the benzyl position (Scheme 99); unfortunately neither of these products could be separated from the biphenyl or bifuran byproducts resulting from homocoupling of the corresponding stannane. However, with addition of 4-methoxyphenylboronic acid **319** and Na_2CO_3, along with heating to 60 °C, a Suzuki–Miyaura coupling could be effected on the aryl bromide leading to isolation of compounds **320** and **321**, both in 73% yield, which demonstrate the selectivity of both catalysts for the benzyl position in Stille cross-couplings.



Scheme 99 Tandem Stille–Suzuki coupling with 4-bromobenzyl chloride **318**.

5.5 Summary

Two new succinimide-containing Pd complexes have been developed and found to be excellent catalysts for Stille cross-couplings with benzyl halides. Both complexes can mediate Stille couplings with a wide range of benzyl chlorides and a high degree of efficiency. They also exhibit an intriguing complementarity with respect to the organostannane used and a remarkable selectivity for benzyl chlorides over aryl bromides.

Part of the work described in this chapter has been included in a publication (see Appendix 1).[250]

Chapter 6: Conclusions and Future Work

6.1 Conclusions

The work described in this thesis has explored new ways of constructing macrocyclic scaffolds containing a variety of unusual functionality. A number of different synthetic routes towards a challenging polyene macrocycle (**91**) have been investigated, based around a Pd-catalysed macrocyclisation strategy. The successful approach utilised a key Wittig reaction with the novel dual nucleophile **209** (Figure 42) to assemble the cyclisation precursor as a single stereoisomer, with a Pd-catalysed allylic Stille reaction used to close the macrocyclic ring and complete the synthesis. The macrocycle **91**, which serves as a model system for a family of pyrone-containing macrocyclic natural products, has therefore been completed in 6.5% overall yield over 11 linear steps, and this has entailed the application of a variety of novel chemical reactions to complex organic systems.

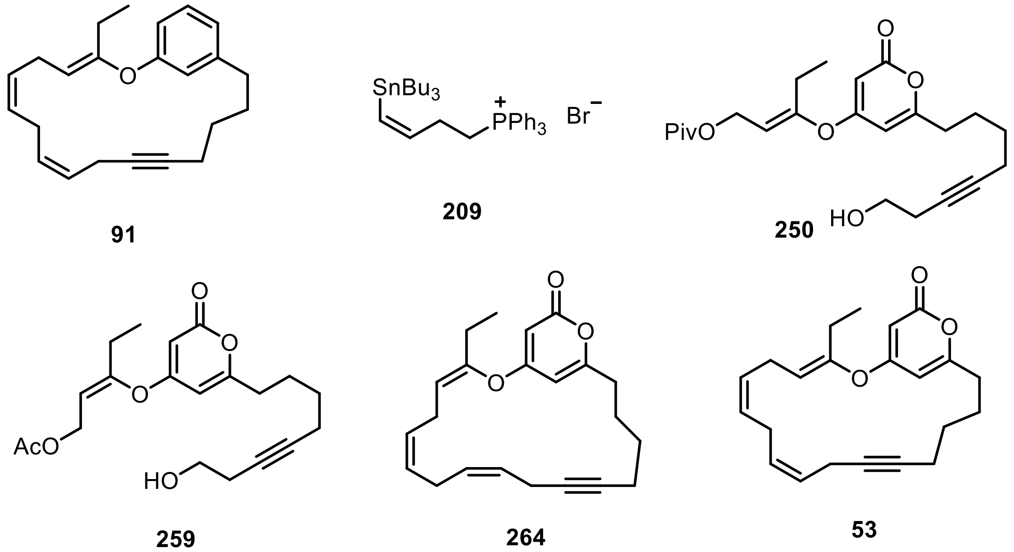
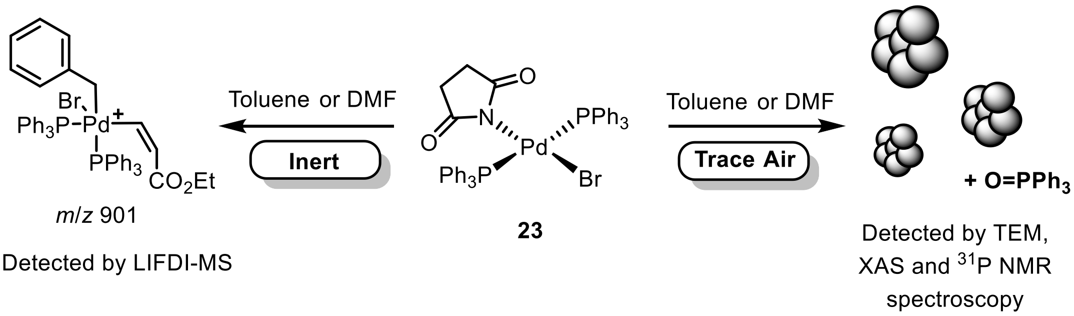


Figure 42 Key compounds **91**, **209**, **250**, **259** and **264** synthesised in this study, along with the originally assigned structure of phacelocarpus 2-pyrone A (**53**).

The retrosynthetic approach established during this initial study has been applied to complete the first total synthesis of the natural product phacelocarpus 2-pyrone A (**264**). Two different and complementary methods for the construction of both the (*E*)- and (*Z*)-isomers of the highly unusual 2-pyronyl enol ether motif have been developed. The (*E*)-enol ether is accessed using an E2 elimination reaction, which has allowed the synthesis of the advanced intermediate **250**. The synthesis of the (*Z*)-isomer uses the highly efficient Au^{I}-catalysed addition of a hydroxypyrone to an internal alkyne, resulting in the key compound **259**. Oxidation, reaction with the phosphonium **209** and Stille macrocyclisation as in the model system has then led to the successful synthesis of the natural product **264**. Spectroscopic studies on the final compound have allowed a reassignment of the stereochemistry around the enol ether bond from the (*E*)-stereoisomer as originally reported (**53**), to a (*Z*)-geometry in the natural compound (**264**).

Further to this, an investigation has been carried out into the role of trace air in certain Stille couplings catalysed by the succinimide-containing Pd complex **23**. This has been investigated in using two model systems, and it has been found that the presence of air can have a dramatic effect, either positive or negative, on the efficiency of the reaction. It is proposed that this is due to a difference in the identity of the active species under different working conditions. Subsequent TEM, XAS, NMR spectroscopy and LIFDI mass spectrometry studies have been carried out in an effort to characterise the active species in each case. These results suggest the formation of Pd nanoparticles upon exposure of the catalyst system to air, and the possibility of a $Pd^{II/IV}$ manifold when no air is present in the system (Scheme 100).



Scheme 100 Possible mechanistic dichotomy with catalyst **23** in the presence or absence of trace air.

Finally, the design, synthesis and testing of two new succinimide-containing Pd complexes has been undertaken. These complexes, AsCat (**229**) and FurCat (**282**) have been applied as catalysts to the Stille cross-coupling reaction of organostannanes with a range of benzyl chlorides and found to be both highly efficient at room temperature, and selective for benzyl chlorides in the presence of aryl bromides. Complex **229** has also been found to be an effective catalyst for the Stille macrocyclisation step leading to compounds **91** and **264**.

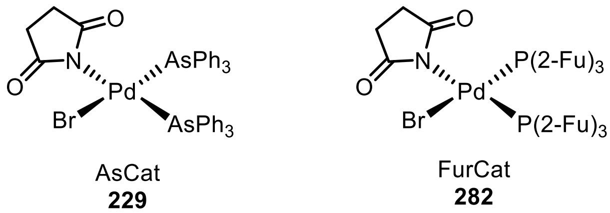


Figure 43 Novel succinimide-containing Pd complexes investigated during this study, **229** and **282**.

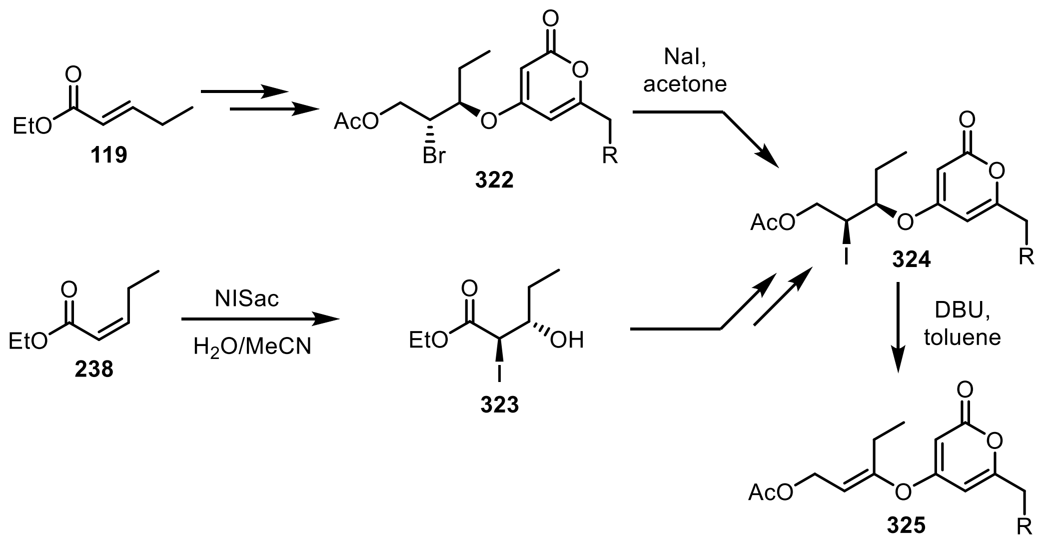
6.2 Future Work

6.2.1 Synthesis of Natural Product and Model System Isomers

Whilst the nOe studies carried out on both the pyrone **264** and aromatic macrocycle **91** strongly support the reassignment of the geometry of the enol ether bond in the natural product, the most effective confirmation would be the synthesis of the alternate isomer of the natural product (**53**).

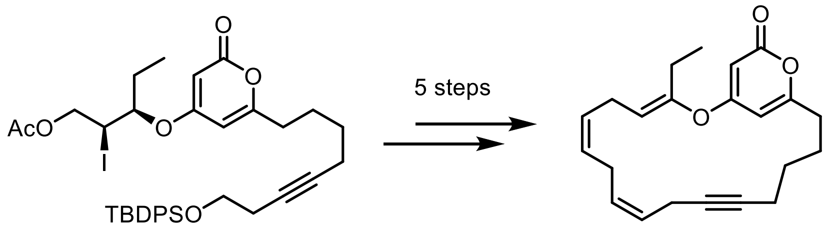
Considerable progress has been made towards delineating a viable synthetic route towards macrocycle **53**, but the key problem which remains to be overcome is finding an efficient and high-yielding route to the (*E*)-pyronyl enol ether substructure. As discussed in Chapter 3, the Mitsunobu–elimination approach has thus far furnished only low yields of the desired product due to the harsh reaction conditions required. Given the failure of the isomerisation attempts (see Chapter 3) of the (*Z*)-stereoisomer, the most promising avenue of investigation would appear to be improving the efficiency of the elimination.

One possible means to do this would be increasing the reactivity of the halide leaving group, thus allowing milder conditions to be employed. The replacement of the bromide with an iodide, which should allow a more facile elimination, gives rise to iodo-ether **324**, and this could be available either directly by iodohydrin formation from an alkene to give **323**, or via the bromide **322** using a Finkelstein reaction (Scheme 101).



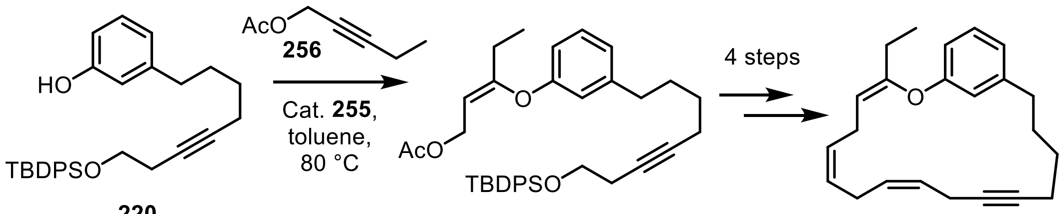
Scheme 101 Proposed syntheses of iodopyronyl ether **324** as a route to the vinyl ether **325**.

Once an efficient and high-yielding route to the pyronylvinylether **326** has been established, the synthesis would be identical to that used for compound **264**, leading to the total synthesis of compound **53** in 10 steps along the longest linear route (Scheme 102).



Scheme 102 Proposed intermediate compound **326**, leading to the total synthesis of macrocycle **53**.

The (*Z*)-isomer of the aromatic model system could also be accessed, using the same strategy used to complete the natural product. This would involve reacting phenol **220** with acetate **256** under Au catalysis to form the (*Z*)-enol ether, and then completion of the synthetic route as before (Scheme 103).

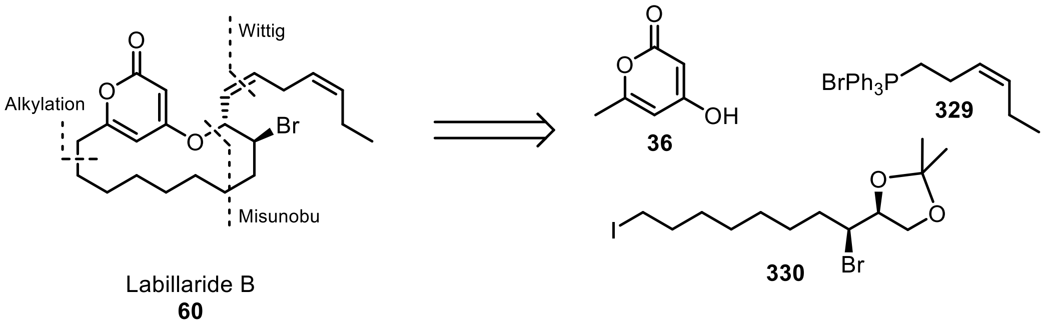


Scheme 103 Proposed synthesis of the (*Z*)-arylvinyl ether **327** as a precursor to macrocycle **328**.

If both isomers were available for both the natural product and the model system, a complete analysis of the stereochemistry could be undertaken, putting the assignment of the stereochemistry of the natural compound beyond all doubt.

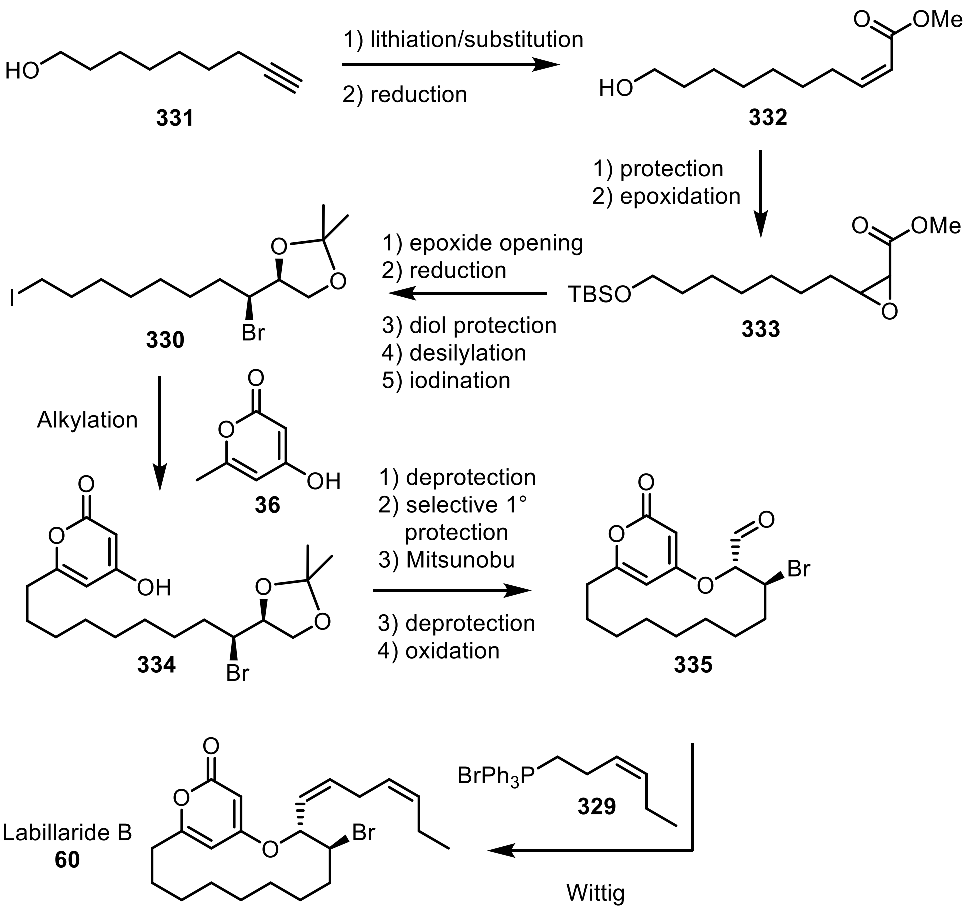
6.2.2 The Total Synthesis of Labillaride B

The chemistry developed in the synthesis of the macrocycles **91** and **264** could be readily applied to the total synthesis of further natural products, especially those in the macrocyclic pyrone family. In particular brominated macrocycle labillaride B (**60**), also isolated from *P. labillaridieri* (see Chapter 1), presents an appealing target.[97] This compound has exhibited some cytotoxic activity in initial biological tests, and no total synthesis has been reported to date. An initial retrosynthetic analysis is shown in Scheme 104.



Scheme 104 Retrosynthetic analysis of labillaride B (**60**)

The skipped diene functionality could be introduced in the final stages of the synthesis using a (*Z*)-selective Wittig reaction and phosphonium salt **329**. A Mitsunobu reaction could be employed to effect the macrocyclisation, with the open-chain precursor constructed using an alkylation reaction of compound **36** with alkyl iodide **330**. This in turn should be available from 8-nonyn-1-ol (**331**). A proposed forward synthesis is shown in Scheme 105.



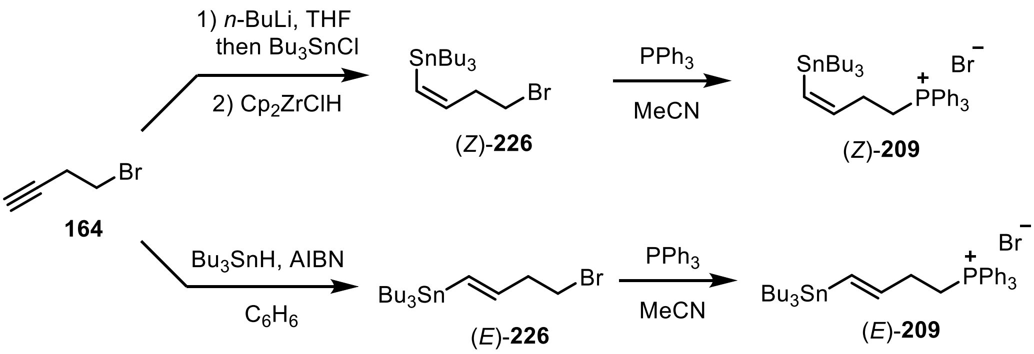
Scheme 105 Proposed forward steps in the synthesis of labillaride B (**60**).

The known[251] starting material **331** could be converted into the iodide **330** using a sequence of well-precedented transformations. This could then be reacted with the dilithiated pyrone species using the method of Hsung,[75] with the primary iodide expected to react in preference to the hindered secondary bromide. Protecting group manipulations would be followed by the key Mitsunobu macrocyclisation. The final steps of the synthesis involve deprotection of the primary alcohol, oxidation to an aldehyde (**335**) and (*Z*)-selective Wittig reaction to give the natural product **60** in 16 steps from a known precursor.

A preliminary study has already been carried out in the Fairlamb group, leading to the successful synthesis of epoxide **333**.[203]

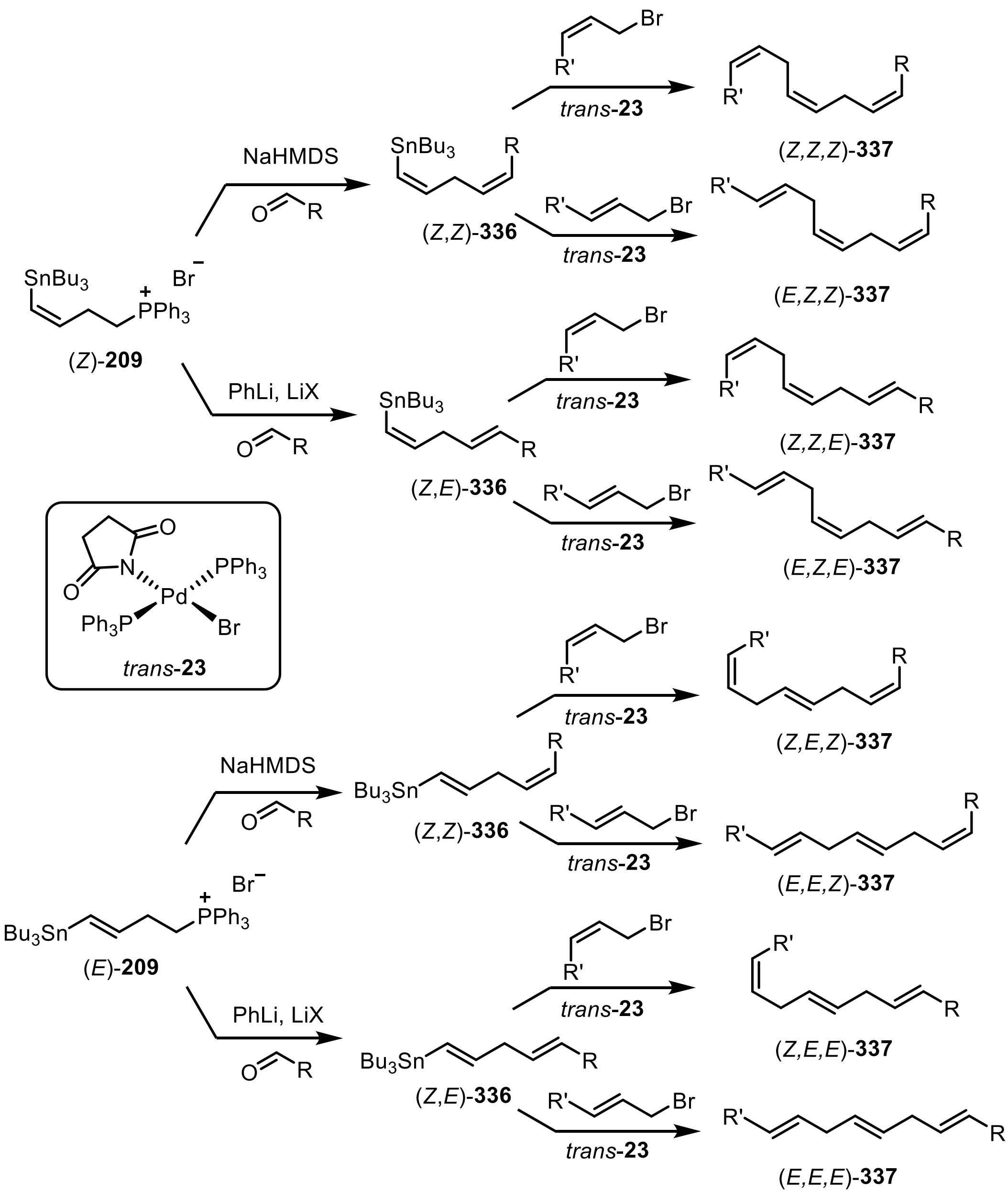
6.2.3 New Methodology for the Synthesis of Skipped Dienes

The skipped diene motif is a prominent feature of many biologically important compounds, meaning that methods for their stereocontrolled synthesis are highly valuable to the field of total synthesis. Whilst a number of methods have been reported for the synthesis of skipped dienes,[252-255] the successful synthesis of bifunctional compound (*Z*)**-209** opens up the potentially powerful combination of the Wittig reaction with Pd catalysed Stille coupling as a new route to skipped dienes.



Scheme 106 Syntheses of (*E*)- and (*Z*)-**209**.

The key reagents **209** should be readily available in both (*E*)- and (*Z*)-isomeric forms in two steps from bromobutyne (**164**, Scheme 106). These could then be employed in either a standard (*Z*)-selective or Schlosser-modified[256] (*E*)-selective Wittig reaction with the appropriate aldehyde, affording a skipped diene with (*E*,*E*)-, (*E*,*Z*)- or (*Z*,*Z*)-geometry containing a vinyl stannane (**336**, Scheme 107). The tributylstannyl group could subsequently be reacted with an allylic or benzylic electrophile in a π-allyl Stille reaction with *trans*-**23** to afford a diverse array of isomeric products (**337**). This approach would allow the possibility to achieve stereocontrol of the double bond at each position in the final compound by the choice of stannane, Wittig conditions and allylic electrophile.



Scheme 107 The use of bifunctional reagents (*E*)- and (*Z*)-**209** in the synthesis of a variety of skipped diene systems.

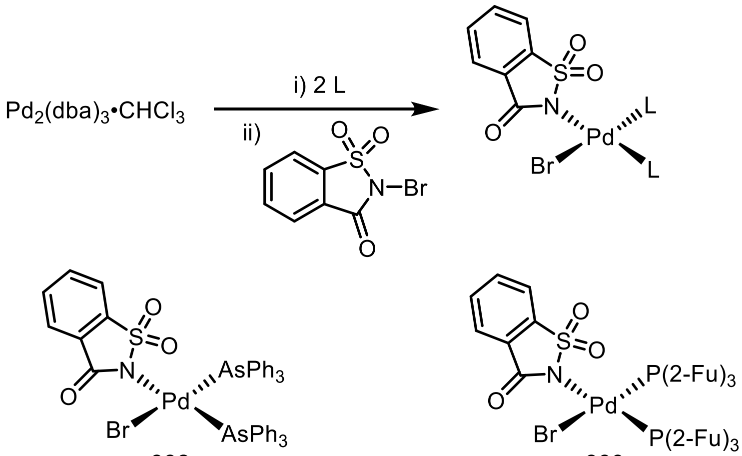
The methodology could also be extended to other cross-coupling reactions (*e.g.* Suzuki–Miyaura) or olefinations (*e.g.* modified Julia or Julia–Kocienski reactions), if the initial screening proves promising.

6.2.4 Second Generation AsCat and FurCat Catalysts

Building on the successful study of the AsCat (**229**) and FurCat (**282**) catalysts described in this thesis, a more detailed mechanistic and kinetic investigation is required to clarify the exact role and significance of the ligands in the low-temperature Stille couplings. A significant expansion of the substrate scope to that already employed can also be envisioned, including to other cross-coupling reactions such as the Suzuki–Miyaura.

In addition to this, a new generation of catalysts could be anticipated, encompassing different imidate ligands in place of succinimide. For example, the saccharin ligand, when used in Pd complexes, has given rise to catalysts which have shown great promise in a variety of cross-couplings with coumarin-based substrates.[257-258] Incorporation of more labile ligands could yield catalysts with enhanced reactivity and selectivity complementary to those catalysts already studied.

The proposed target complexes, **338** and **339**, could be synthesised in a similar fashion to the succinimide-based catalysts, by reacting $Pd_2(dba)_3{\cdot}CHCl_3$ with two equivalents of the appropriate ligands, followed by oxidative addition with *N*-bromosaccharin (Scheme 108).



Scheme 108 Structure and proposed synthesis of new saccharin-based Pd complexes **338** and **339**.

The reactivity of these new complexes could be analysed in comparison with the two complexes already studied in order to attempt to explain the role of the imidate ligand.

Chapter 7: Experimental Section

7.1 General Experimental Techniques

Solvents and Reagents

Commercially sourced reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros Organics or Fluorochem and used as received unless otherwise noted. Dry ether (diethyl ether), THF, dichloromethane, hexane, toluene and acetonitrile were obtained from a Pure Solv MD-7 solvent machine and stored under nitrogen. Ether and THF were also degassed by bubbling nitrogen gas through the solvent with sonication. Dry pyridine, triethylamine and TMEDA were obtained by distillation from KOH and stored under nitrogen. Dry acetone and cyclohexane were obtained by distillation from CaH_2 and stored under nitrogen. Dry DMF and DMSO were purchased from Acros Organics; DMF was degassed by bubbling nitrogen gas through the solvent with sonication, DMSO was used as received. Petrol refers to the fraction of petroleum ether boiling in the range 40–60 °C.

Reactions requiring anhydrous or air-free conditions were carried out in dry solvent under an argon or nitrogen atmosphere using oven- or flame-dried glassware.

MEPI-Pd (**174**),[149] $Pd_2dba_3{\cdot}CHCl_3$,[154] $PdCl_2(MeCN)_2$,[259] ABCat,[157] nosylhydrazide,[162] dipotassium azo-1,2-dicarboxylate[163] and $PdCl_2(PPh_3)_2$[213] were synthesised following literature procedures. $[(AuIPr)_2(\mu\text{-}OH)][BF_4]$ (**255**) was generously provided by Prof. S. Nolan.

Chromatography

Thin layer chromatography (TLC) was carried out using Merck aluminium backed 5554 plates. Spots were visualised by the quenching of ultraviolet light (λ_{max} = 254 nm) and then stained and heated with a solution of anisaldehyde, potassium permanganate or phosphomolybdic acid as appropriate. Retention factors (R_f) are reported along with the solvent system used in parentheses. Flash column chromatography was ordinarily performed using Merck 60 silica gel (particle size 40–63 µm); where indicated it was performed using SiO_2–K_2CO_3 (9:1, *w*/*w*) as the stationary phase in order to remove tin-containing impurities.[244] Preparatory TLC was carried out using Analtech UNIPLATE glass-backed silica plates. The solvent system used in each case is reported in parentheses.

Melting Points

Melting points were determined using a Stuart SMP3 melting point apparatus using a temperature ramp of 3 °C min^{-1}.

Infrared Spectroscopy

Infrared spectra were recorded using a Thermo-Nicolet Avatar-370 FT-IR spectrometer, or a PerkinElmer Spectrum Two spectrometer using an UATR attachment. They were carried out as either a KBr disc, solution, thin film or ATR as reported in the text. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and are described as strong (s), medium (m), weak (w) or broad (br). Where indicated, reactions were monitored *in situ* using a Mettler Toledo ReactIR ic10 with a k6 conduit SiComp (silicon) probe and MCT detector.

Nuclear Magnetic Resonance Spectroscopy

Proton (^{1}H) and Carbon-13 (^{13}C) NMR spectra were recorded on one of a Jeol ECX400 or Jeol ECS400 spectrometer at 400 and 100 MHz respectively, a Bruker AV500 operating at 500 and 125 MHz respectively, or a Bruker AV700 operating at 700 and 175 MHz respectively. The ^{13}C NMR spectrum of compound **264** was recorded on a Bruker AVIII800 spectrometer (Manchester Institute of Biotechnology) operating at 200 MHz. Chemical shifts are reported in parts per million (ppm) of tetramethylsilane using residual solvent as an internal standard ($CHCl_3$ δ_H = 7.26 ppm; $CDCl_3$ δ_C = 77.16 ppm). Multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), multiplet (m), apparent (app.) and broad (br). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Spectra were processed using MestreNova and, where required, exported as JPEG images into the appropriate document. Copies of ^{1}H and ^{13}C NMR spectra for all compounds are given in Appendix 7.

Boron-11 (^{11}B) spectra were recorded on a Jeol ECS400 spectrometer at 128 MHz. Chemical shifts are referenced externally to $BF_3{\cdot}OEt_2$ and reported in parts per million (ppm).

Fluorine-19 (^{19}F) spectra were recorded on a Jeol ECX400 or Jeol ECS400 spectrometer at 376 MHz. Chemical shifts are referenced externally to $CFCl_3$ and reported in parts per million (ppm).

Phosphorus-31 (^{31}P) spectra were recorded on a Jeol ECX400 or Jeol ECS400 spectrometer at 162 MHz. Chemical shifts are referenced externally to H_3PO_4 and reported in parts per million (ppm).

Tin-119 (^{119}Sn) spectra were recorded on a Bruker AV500 spectrometer at 187 MHz. Chemical shifts are referenced externally to $SnCl_4$ and reported in parts per million (ppm).

Mass Spectrometry

Electrospray ionisation (ESI) mass spectrometry was performed on a Bruker daltronics micrOTOF spectrometer. Electron impact (EI), atmospheric pressure chemical ionisation (APCI) and liquid induction field desorption ionisation (LIFDI) mass spectrometry were performed on a Waters GCT Premier mass spectrometer. Mass to charge ratios (m/z) are reported in Daltons with percentage abundance in parentheses along with the corresponding fragment ion, where known. High resolution mass spectra (HRMS) are reported with less than 5 ppm error.

UV–Visible Spectroscopy

UV–visible spectroscopy was performed on a Jasco V-560 spectrometer, with a background taken in the appropriate solvent prior to recording spectra, using a cell with a path length of 1 cm. The wavelength of maximum absorption (λ_{max}) is reported in nm along with the extinction coefficient (ε) in $dm^3\ mol^{-1}\ cm^{-1}$. Copies of the appropriate absorption spectra and Beer–Lambert plots are given in Appendix 6.

Elemental Analysis

Elemental analysis was carried out using an Exeter Analytical CE-440 Elemental Analyser, with the percentages reported as an average of two runs.

X-Ray Crystallography

Diffraction data were collected at 110 K on an Agilent SuperNova diffractometer with Mo Kα radiation (λ = 0.71073 Å). Data collection, unit cell determination and frame integration were carried out with CrysalisPro. Absorption corrections were applied using face indexing and the ABSPACK absorption correction software within CrysalisPro. Structures were solved and refined using Olex2[260] implementing SHELX algorithms and the Superflip[261-263] structure solution program. Structures were solved by charge flipping, Patterson or direct methods and refined with the ShelXL[264] package using full-matrix least squares minimisation. All non-hydrogen atoms were refined anisotropically. Tables of crystallographic data are given in Appendix 3.

Transmission Electron Microscopy

Transmission election microscopy was performed at the Department of Biology Technology Facility, University of York, using an FEI Tecnai 12 G2 BioTWIN microscope operating at 120 kV, and images were captured using SIS Megaview III camera. Samples were suspended in ethanol and applied to a TEM grid with a Formvar/carbon film. The resulting images were enlarged and particles measured manually.

7.2 General Procedures

General Procedure A: Synthesis of Succinimide Catalysts

To a Schlenk tube containing $Pd_2dba_3{\cdot}CHCl_3$ (1 eq.) and ligand L (4 eq.) under N_2 was added dry CH_2Cl_2 (70 mL mmol^{-1}), and the resulting mixture was stirred for 10 min at RT, resulting in a clear orange to brown solution. After this time, a solution of *N*-bromosuccinimide (recrystallized from H_2O and dried *in vacuo*, 2 eq.) in dry CH_2Cl_2 (20 mL mmol^{-1}) was added in one portion and the reaction mixture stirred for a further 10 min. The resulting yellow to orange solution was diluted with petroleum ether (*ca*. 1.5 L mmol^{-1}) to precipitate the complex. The yellow-to-pale-brown solid was filtered off, washed with petrol and dried *in vacuo* to afford the desired compound. Complexes could be purified, if needed, by dissolving in the minimum volume of CH_2Cl_2 and precipitating with ether.

General Procedure B: Stille cross-coupling reactions with benzyl bromide for air-effect studies

A Schlenk tube (for dimensions see Section 4.2, Chapter 4) containing *cis*- or *trans*-$(Ph_3P)_2Pd$(*N*-succ)Br **23** (4.7 mg, 5.8 μmol) and a stirrer bar was evacuated and backfilled with N_2 three times. A solution of stannane (*E*)- or (*Z*)-**278** (50 mg, 0.13 mmol) in dry, degassed DMF (1.5 mL) was added, followed by benzyl bromide (14 μL, 20 mg, 0.12 mmol). The reaction mixture was then treated in one of two ways: (a) the flow of N_2 was closed at the Schlenk side-arm and the stopper was removed for five seconds (timed with a stopwatch) with rapid stirring, before being replaced and the vessel left sealed; (b) the Schlenk tube was sealed under a flow of N_2. The reactions were then heated to the specified temperature and stirred for 3 h. The resulting solution was cooled to RT, the solvent removed *in vacuo* and the crude residue analysed by ^{1}H NMR spectroscopy or other methods as appropriate.

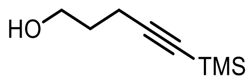
General procedure C: Room-temperature Stille cross-coupling reactions with benzyl chlorides

To a solution of the appropriate catalyst (5.84 μmol, 0.05 eq.) and benzyl halide (0.117 mmol, 1 eq.) in dry DMF (1.5 mL) under N_2 in a Schlenk tube was added the appropriate stannane (0.176 mmol, 1.5 eq.). The reaction vessel was sealed and stirred at RT for the required time. After this time the solution was diluted with ether (20 mL), washed with water (3 × 10 mL), dried ($MgSO_4$), filtered and evaporated. When purification was performed, it was carried out using flash column chromatography with a SiO_2–K_2CO_3 (9:1, *w*/*w*) stationary phase and the solvent system specified for each compound.

7.3 Synthetic Procedures and Compound Data

Throughout this section, laboratory notebook references are given for the experiment from which the synthetic procedure is quoted. Where reactions were not optimised by the author, both the initial test reaction details and the optimised procedure are given, along with both notebook references. For experiment references for specific NMR data, see the relevant NMR spectra in Appendix 7. Known compounds are indicated with a literature reference next to the compound name.

1-Trimethylsilyl-2-pentyn-5-ol (110)[109]

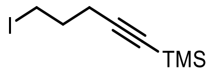


To a solution of 4-pentyn-1-ol (500 mg, 5.94 mmol) in dry THF (20 mL) at −78 °C was added dropwise *n*-butyllithium (2.33 M in hexanes, 5.10 mL, 11.9 mmol), and the resulting white suspension was stirred for 1 h. The reaction was then quenched by the addition of chlorotrimethylsilane (1.59 mL, 12.5 mmol) and allowed to warm to RT over 2 h. After this time the solution was poured into a mixture of ether (15 mL) and 10% aq. HCl (15 mL) and stirred vigorously overnight. The layers were separated and the aqueous phase was extracted with ether (2 × 30 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, CH_2Cl_2→CH_2Cl_2/MeOH, 99:1, *v*/*v*) afforded the *title compound* as a colourless oil (848 mg, 91%).

R_f 0.38 (ether/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3332br, 2957m, 2175m, 1431w, 1249s, 1051m, 984w, 925w, 836s, 758s, 697m, 639m, 581w; ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (q, J = 5.5 Hz, 2H), 2.34 (t, J = 6.9 Hz, 2H), 1.76 (quin, J = 6.5 Hz, 2H), 1.57 (br d, J = 3.2 Hz, 1H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.7, 85.4, 62.1, 31.2, 16.7, 0.2; MS (ESI$^+$) *m/z* (rel. %) 179 ([M+Na]$^+$, 65), 157 ([M+H]$^+$, 100); HRMS (ESI$^+$) 157.1041 [M+H]$^+$, $C_8H_{17}OSi$ requires 157.1043.

Lab book reference number: TOR-1-39

1-Trimethylsilyl-5-iodo-2-pentyne (100)[109]

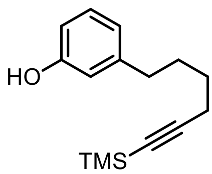


To a solution of alcohol **110** (1.38 g, 8.80 mmol) in ether (36 mL) and MeCN (12 mL) was added triphenylphosphine (2.54 g, 9.68 mmol) and imidazole (659 mg, 9.68 mmol). The resultant solution was cooled to 0 °C and iodine (2.46 g, 9.68 mmol) was added. The reaction mixture was stirred at RT for 6 h during which time a white precipitate formed. The reaction was then cooled to 0 °C, filtered and concentrated *in vacuo*. Ether (100 mL) was added, and the organic solution was washed with 10% aq. $Na_2S_2O_3$ (60 mL). The layers were separated and the aqueous layer was extracted with ether (60 mL), and the combined organic layers were then washed with brine (60 mL), dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, heptane/ether, 98:2, *v*/*v*) afforded the *title compound* as a colourless oil (2.07 g, 88%).

R_f 0.67 (ether/petrol, 1:9, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2958m, 2859w, 2175m, 1428w, 1323w, 1248s, 1221w, 1168w, 1021w, 1031w, 836s, 758s, 698m, 638m, 572w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.29 (t, *J* = 6.8 Hz, 2H), 2.36 (t, *J* = 6.8 Hz, 2H), 2.00 (quin, *J* = 6.8 Hz, 2H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 105.0, 85.9, 32.1, 21.0, 5.30, 0.17.

Lab book reference number: TOR-4-324

3-(6-Trimethylsilyl-5-hexynyl)phenol (101)

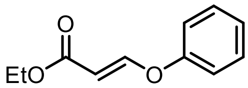


To a solution of TMEDA (235 µL, 1.58 mmol) in dry hexane (5 mL) at −78 °C was added dropwise *n*-butyllithium (2.3 M in hexane, 0.68 mL, 1.58 mmol), followed by potassium *tert*-butoxide (177 mg, 1.58 mmol) in one portion. The reaction mixture was warmed to −20 °C and *m*-cresol (66 µL, 0.63 mmol) added. After 3.5 h, the cooling bath was removed, dry THF (2 mL) added, and the reaction cooled to −78 °C before a solution of iodide **100** (200 mg, 0.75 mmol) in dry THF (1 mL) was added. The cooling bath was then removed, and the reaction stirred for 1 h before being quenched with water (5 mL) and 6 M aq. HCl (1.2 mL). The layers were separated, and the aqueous layer extracted with ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 9:1, *v/v*) afforded the *title compound* as a colourless oil (103 mg, 76%).

R_f 0.18 (ether/petrol, 1:4, *v/v*); IR ($CHCl_3$, cm^{-1}) ν_{max} 3378br, 2940m, 2900w, 2860w, 2173m, 1598m, 1589m, 1487w, 1455m, 1249s, 1155m, 842s, 781m, 760s, 696s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.10 (m, 1H), 6.75 (dq, J = 8.1, 0.8 Hz, 1H), 6.67–6.59 (m, 2H), 4.74 (br s, 1H), 2.57 (t, J = 7.6 Hz, 2H), 2.23 (t, J = 7.1 Hz, 2H), 1.70 (tt, J = 8.6, 6.7 Hz, 2H), 1.58–1.49 (m, 2H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 144.5, 129.6, 121.1, 115.4, 112.8, 107.5, 84.8, 35.3, 30.4, 28.2, 19.9, 0.3; MS (ESI^+) *m/z* (rel. %) 269 ($[M+Na]^+$, 30), 247 ($[M+H]^+$, 100); HRMS (ESI^+) 247.1512 $[M+H]^+$, $C_{15}H_{23}OSi$ requires 247.1513.

Lab book reference number: TOR-1-56

Ethyl (2*E*)-3-phenoxyprop-2-enoate (113)[265]

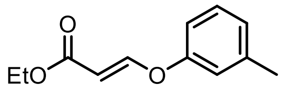


A solution of ethyl propiolate (200 mg, 2.04 mmol), phenol (192 mg, 2.04 mmol) and DABCO (22.5 mg, 0.20 mmol) in CH_2Cl_2 (12 mL) was stirred at RT for 10 min. After this time, the solvent was removed *in vacuo* and the residue purified by flash chromatography (SiO_2, petrol/ether, 19:1, *v/v*), affording the *title compound* as a yellow oil (379 mg, 97%).

R_f 0.83 (EtOAc/petrol, 2:3, *v/v*); IR (thin film, cm^{-1}) ν_{max} 2982w, 1709s, 1649s, 1632m, 1588s, 1488s, 1368w, 1319m, 1210s, 1186s, 1167s, 1110s, 1044m, 950m, 835m, 756s, 690s, 492w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 12.2 Hz, 1H), 7.43–7.32 (m, 2H), 7.22–7.16 (m, 1H), 7.12–7.02 (m, 2H), 5.55 (d, J = 12.2 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 159.2, 156.0, 130.1, 125.1, 118.2, 102.3, 60.2, 14.5; MS (ESI^+) *m/z* (rel. %) 215 ($[M+Na]^+$, 100), 193 ($[M+H]^+$, 95); HRMS (ESI^+) 215.0678 $[M+Na]^+$, $C_{11}H_{12}NaO_3$ requires 215.0679.

Lab book reference number: TOR-1-1

Ethyl (2*E*)-3-(3-methylphenoxy)prop-2-enoate (114)

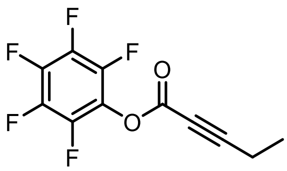


A solution of ethyl propiolate (200 mg, 2.04 mmol), *m*-cresol (220 mg, 2.04 mmol) and DABCO (22.5 mg, 0.20 mmol) in CH_2Cl_2 (12 mL) was stirred at RT for 24 h. After this time, the solvent was removed *in vacuo* and the residue purified by flash chromatography (SiO_2, petrol/ether, 19:1→9:1, *v*/*v*), affording the *title compound* as a colourless oil (221 mg, 53%).

R_f 0.69 (ether/petrol, 1:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2981w, 1710s, 1650s, 1608m, 1584s, 1488m, 1462w, 1368w, 1295w, 1247s, 1178m, 1108s, 1144s, 1043m, 951m, 839m, 780m, 689m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 12.2 Hz, 1H), 7.25 (td, J = 7.6, 0.6 Hz, 1H), 7.06–6.94 (m, 1H), 6.92–6.83 (m, 2H), 5.53 (d, J = 12.2 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 2.36 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 159.4, 156.0, 140.4, 129.8, 125.9, 118.8, 115.2, 102.1, 60.2, 21.5, 14.5 ; MS (ESI$^+$) *m*/*z* (rel. %) 229 ($[M+Na]^+$, 100), 207 ($[M+H]^+$, 25); HRMS (ESI$^+$) 229.0827 $[M+Na]^+$, $C_{12}H_{14}NaO_3$ requires 229.0835.

Lab book reference number: TOR-1-4

Pentafluorophenyl 2-pentynoate (117)

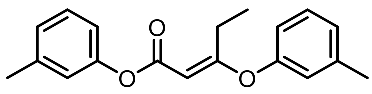


2-Pentynoic acid (200 mg, 2.04 mmol) and pentafluorophenol (413 mg, 2.24 mmol) were dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C. DCC (462 mg, 2.24 mmol) was added and the reaction mixture was stirred for 6 h at RT before being filtered and concentrated *in vacuo*. Flash chromatography (SiO_2, petrol/ether, 99:1, *v*/*v*) afforded the *title compound* as a colourless oil (502 mg, 93%).

R_f 0.63 (EtOAc/petrol, 3:7, *v*/*v*); IR ($CDCl_3$, cm^{-1}) ν_{max} 2257m, 2224m, 1752m, 1521s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (q, J = 7.5 Hz, 2H), 1.27 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) 148.9, 141.2 (ddq, $J_{C–F}$ = 252.9, 12.8, 4.2 Hz), 140.0 (dtt, $J_{C–F}$ = 253.8, 13.3, 3.8 Hz), 138.0 (dm, $^1J_{C–F}$ = 249.0 Hz), 124.6–124.1 (m), 96.8, 70.3, 12.9, 12.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −151.7–−152.3 (m, 2F), −157.0 (t, J = 21.5 Hz, 1F), −161.5–−162.2 (m, 2F); MS (LIFDI$^+$) *m*/*z* (rel. %) 183 ($[M-C_5H_5O]^+$, 80), 81 ($[M-C_6F_5O]^+$, 100).

Lab book reference number: TOR-1-5

3-Methylphenyl (2*E*)-3-(3-methylphenoxy)pent-2-enoate (118)

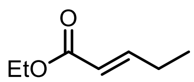


A solution of alkyne **117** (30 mg, 0.11 mmol), *m*-cresol (12 mg, 0.11 mmol) and DABCO (2.6 mg, 0.023 mmol) in CH_2Cl_2 (1.5 mL) was stirred at RT for 5.5 h, after which time the solvent was removed *in vacuo*. Flash chromatography (SiO_2, petrol→petrol/ether, 99:1, *v*/*v*) afforded the *title compound* as a colourless oil (7 mg, 27%).

R_f 0.71 (ether/petrol, 1:4, *v*/*v*); IR ($CHCl_3$, cm^{-1}) ν_{max} 3684m, 3047w, 2922m, 1726s, 1620s, 1582m, 1485m; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (td, *J* = 7.5, 1.1 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.06 (dd, *J* = 6.9, 1.3 Hz, 1H), 7.01–6.94 (m, 1H), 6.89–6.77 (m, 4H), 4.96 (s, 1H), 2.96 (q, *J* = 7.5 Hz, 2H), 2.38 (s, 3H), 2.32 (s, 3H), 1.29 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.00, 166.14, 153.37, 150.75, 140.45, 139.47, 129.83, 129.06, 126.74, 126.31, 122.52, 122.13, 118.84, 118.51, 94.03, 25.32, 21.41, 21.38, 11.88; MS (ESI^+) *m*/*z* (rel. %) 297 ($[M+H]^+$, 20), 319 ($[M+Na]^+$, 100); HRMS (ESI^+) 319.1296 $[M+Na]^+$, $C_{19}H_{20}NaO_3$ requires 319.1305.

Lab book reference number: TOR-1-10

Ethyl (*E*)-2-pentenoate (119)[266]

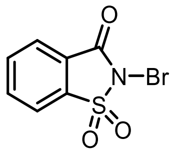


A solution of (*E*)-2-pentenoic acid (500 mg, 5.0 mmol), and concentrated H_2SO_4 (0.1 mL) in EtOH (5 mL) was stirred under reflux for 18 h. The reaction mixture was cooled to RT, and the solvent evaporated *in vacuo,* before the addition of water (15 mL). The resulting aqueous solution was extracted with ether (4 × 25 mL), and the combined organic layers dried over $MgSO_4$, filtered and evaporated, with no heating, to afford the *title compound* as a volatile colourless oil, which was used without further purification (634 mg, 99%).

R_f 0.64 (ether/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2973m, 1717s, 1654m, 1462w, 1368m, 1333m, 1264m, 1179s, 1124m, 1042s, 978m, 912w, 859m, 710w; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (dt, *J* = 15.7, 6.4 Hz, 1H), 5.80 (dt, *J* = 15.7, 1.7 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.30–2.12 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.06 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 150.8, 120.5, 60.2, 25.4, 14.4, 12.3.

Lab book reference number: TOR-1-16

***N*-Bromosaccharin (125)**[267]

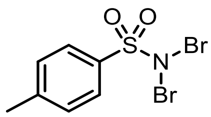


To a solution of sodium saccharin (25 g, 103.6 mmol), Na_2CO_3 (5.5 g, 51.8 mmol) and KBr (12.3 g, 103.6 mmol) in water (500 mL) with mechanical stirring was added a solution of oxone (63.7 g, 103.6 mmol) in water (60 mL) at 0 °C, over 1 h using a dropping funnel. The cooling was removed and the reaction mixture stirred at RT for 24 h, after which time it was cooled to 0 °C and the resulting precipitate filtered, washed with ice-cold water and dried *in vacuo* to give the *title compound* as a white solid (25.7 g, 95%).

M.P. 180–183 °C (lit.[267] 177.5–181 °C); IR (KBr, cm^{-1}) ν_{max} 3093m, 1639s, 1584s, 1458m, 1334m, 1254s, 1153s, 1052m, 958s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–8.07 (m, 1H), 7.99–7.93 (m, 1H), 7.90 (td, *J* = 7.6, 1.5 Hz, 1H), 7.85 (td, *J* = 7.5, 1.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 138.4, 135.2, 134.8, 127.2, 125.9, 121.8; MS (ESI$^+$) *m*/*z* (rel. %) 228 ($[M-Br+2Na]^+$, 100), 206 ($[M-Br+H+Na]^+$, 25), 184 ($[M-Br+2H]^+$, 80).

Lab book reference number: TOR-8-697

***N,N*-Dibromo-*p*-toluenesulfonamide (126)**[268]

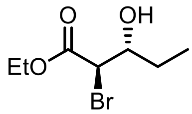


To a solution of *p*-toluenesulfonamide (5 g, 29.2 mmol) and Na_2CO_3 (3.4 g, 32.1 mmol) in water (25 mL) with vigorous stirring was added bromine (3.0 mL, 58.4 mmol), resulting in the formation of a thick precipitate. After 2 h, the precipitate was filtered, washed with ice-cold water and dried *in vacuo* to afford the *title compound* as a yellow solid (8.18 g, 85%).

M.P. 94–95 °C (lit.[269] 92–93 °C); IR (KBr, cm^{-1}) ν_{max} 3060w, 2985w, 1925w, 1596s, 1491m, 1447m, 1406m, 1359s, 1107s, 1083s, 814s, 742s, 659s, 561s; ^{1}H NMR (400 MHz, C_6D_6) δ 7.81 (d, *J* = 8.0 Hz, 2H), 6.70 (d, *J* = 8.0 Hz, 2H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 145.9, 136.8, 131.0, 128.0, 20.9; MS (ESI$^+$) *m*/*z* (rel. %) 194 ($[M-2Br+2H+Na]^+$, 100), 172 ($[M-2Br+3H]^+$, 20).

Lab book reference number: TOR-1-25

Ethyl (2*R, 3*R**)-2-bromo-3-hydroxypentanoate (127)**[270]

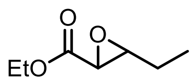


To a solution of ester **119** (300 mg, 2.34 mmol) in MeCN (4 mL) and water (1 mL) was added *N*-bromosaccharin **125** (675 mg, 2.57 mmol) in one portion. The resulting solution was stirred for 2 h at RT before being diluted with ether (30 mL). The reaction mixture was washed successively with sat. aq. $NaHCO_3$ (20 mL), sat. aq. $Na_2S_2O_3$ (20 mL) and water (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (SiO_2, petrol/ether, 85:15, *v*/*v*) afforded the *title compound* as a colourless oil (349 mg, 66%).

R_f 0.45 (ether/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3450br, 2977m, 2938w, 2880w, 1726s, 1464m, 1372m, 1280s, 1184s, 1148s, 1097m, 1035s, 972s, 894w, 856w, 803w, 643w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (q, *J* = 7.2 Hz, 2H), 4.12 (d, *J* = 7.7 Hz, 1H), 3.93 (dddd, *J* = 8.6, 7.7, 6.2, 3.2 Hz, 1H), 2.69 (d, *J* = 6.2 Hz, 1H), 1.87 (dqd, *J* = 14.9, 7.4, 3.2 Hz, 1H), 1.53 (ddq, *J* = 14.9, 8.6, 7.4 Hz, 1H), 1.29 (t, *J* = 7.2, 3H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 73.7, 62.3, 47.8, 26.5, 14.0, 9.7; MS (ESI$^+$) *m*/*z* (rel. %) 247 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 246.9943 [M+Na]$^+$, $C_7H_{13}BrNaO_3$ requires 246.9940.

Lab book reference number: TOR-1-29

Ethyl 2,3-epoxypentanoate (130)[271]

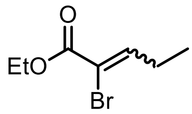


Bromohydrin **127** (50 mg, 0.22 mmol), 4-bromo-6-methyl-2-pyrone (46 mg, 0.24 mmol) and triethylamine (34 µL, 0.24 mmol) were dissolved in CH_2Cl_2 (2 mL) and heated to reflux for 7 h, then stirred at RT for 17 h. After this time the solvent was removed *in vacuo*. Flash chromatography (SiO_2, petrol/ether, 80:20, *v*/*v*) afforded the *title compound* as a colourless oil (16 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29–4.15 (m, 2H), 3.21 (d, *J* = 1.9 Hz, 1H), 3.14 (ddd, *J* = 6.0, 4.9, 1.9 Hz, 1H), 1.75–1.57 (m, 2H), 1.29 (td, *J* = 7.1, 0.5 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 61.6, 59.5, 52.9, 24.6, 14.2, 9.6; MS (ESI$^+$) *m*/*z* (rel. %) 167 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 167.0674 [M+Na]$^+$, $C_7H_{12}NaO_3$ requires 167.0679.

Lab book reference number: TOR-1-30

Ethyl 2-bromopent-2-enoate (132)[272]

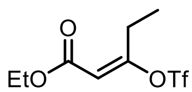


Bromohydrin **127** (100 mg, 0.44 mmol), *m*-cresol (70 µL, 0.67 mmol) and triphenylphosphine (175 mg, 0.67 mmol) were dissolved in dry THF (2 mL) and cooled to 0 °C. DIAD (131 µL, 0.67 mmol) was added and the resulting solution stirred at RT for 21 h. The solvent was removed *in vacuo*, and the resulting residue taken up in ether (5 mL) and filtered. The filtrate was concentrated *in vacuo*. Flash chromatography (SiO_2, ether/petrol, 1:4, *v*/*v*) afforded the *title compound* as a yellow oil (35 mg, 38%, *E*/*Z* = 1:1).

All data is quoted for a mixture of both geometrical isomers.
R_f 0.58 (ether/petrol, 1:4, *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.1 Hz, 1H), 6.65 (t, *J* = 7.8 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.49 (quin, *J* = 7.6 Hz, 2H), 2.34 (quin, *J* = 7.5 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.6 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 162.7, 150.0, 147.5, 115.9, 110.9, 62.5, 62.2, 25.7, 25.1, 14.3, 14.2, 13.3, 12.0; MS (ESI$^+$) *m*/*z* (rel. %) 207 ([M+H]$^+$, 100); HRMS (ESI$^+$) 207.0015 [M+H]$^+$, $C_7H_{12}BrO_2$ requires 207.0015.

Lab book reference number: TOR-1-32

Ethyl (*E*)-3-(trifluoromethylsulfonyloxy)pent-2-enoate (*E*-134)[129]

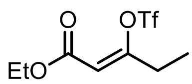


To a solution of ethyl propionylacetate (3.31 g, 23.0 mmol) in hexane (116 mL) was added water (29 mL), and the resulting biphasic mixture was cooled to 5 °C with rapid stirring. Tetramethylammonium hydroxide (25 wt% aq., 41.9 mL, 115 mmol) was added and the biphasic mixture was vigorously stirred for *ca*. 10 min, followed by dropwise addition of triflic anhydride (9.7 mL, 57.4 mmol). After 20 min, the reaction mixture was diluted with water (120 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2 × 100 mL), and the combined organic layers were washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 19:1, *v*/*v*) afforded the *title compound* as a colourless oil (4.04 g, 63%).

R_f 0.70 (ether/petrol, 1:1, *v*/*v*); IR ($CHCl_3$, cm^{-1}) ν_{max} 2926m, 2855w, 1729m, 1666w, 1425m, 1374w, 1246m, 1214s, 1143s, 1112m, 1026m, 963s, 881w, 855m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.94 (q, *J* = 7.5 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 164.2, 120.1 (q, $^1J_{C–F}$ = 320.1 Hz), 112.2, 61.3, 25.2, 14.2, 10.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.9; MS (ESI$^+$) *m*/*z* (rel. %) 277 ([M+H]$^+$, 100); HRMS (ESI$^+$) 277.0357 [M+H]$^+$, $C_8H_{12}F_3O_5S$ requires 277.0352.

Lab book reference number: TOR-4-312

Ethyl (*Z*)-3-(trifluoromethylsulfonyloxy)pent-2-enoate (*Z*-134)[129]

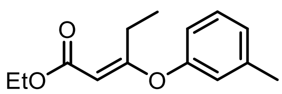


Title compound was isolated as a side product during the synthesis of triflate (*E*)**-134** (37 mg, 10%).

R_f 0.47 (ether/petrol, 1:1, *v*/*v*); IR ($CHCl_3$, cm^{-1}) ν_{max} 2983w, 2927m, 1732s, 1681m, 1427s, 1371w, 1303m, 1206s, 1190s, 1142s, 1030m, 943w, 916s, 857m, 655w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (t, *J* = 1.3 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.42 (qd, *J* = 7.3, 1.3 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 160.3, 118.4 (q, $^1J_{C–F}$ = 319.9 Hz), 111.1, 61.4, 27.8 (q, $^5J_{C–F}$ = 2.3 Hz), 14.1, 10.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.6; MS (ESI$^+$) *m*/*z* (rel. %) 299 ([M+Na]$^+$, 100), 277 ([M+H]$^+$, 45); HRMS (ESI$^+$) 277.0349 [M+H]$^+$, $C_8H_{12}F_3O_5S$ requires 277.0352.

Lab book reference number: TOR-1-35

Ethyl (*E*)-3-(3-methylphenoxy)pent-2-enoate (116)

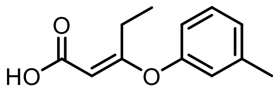


A flame-dried Schlenk tube containing a stirrer bar was charged with triflate ***E*-134** (100 mg, 0.359 mmol) and K_3PO_4 (153 mg, 0.719 mmol) before being evacuated and backfilled with nitrogen. Dry toluene (2 mL) was added, followed by a premixed solution of $Pd(OAc)_2$ (4.0 mg, 0.018 mmol) and X-Phos (8.6 mg, 0.018 mmol) in dry toluene (0.5 mL). Transfer was made quantitative with an additional portion of dry toluene (0.5 mL). Finally *m*-cresol (45 µL, 0.431 mmol) was added *via* syringe and the reaction heated to 100 °C for 24 h. The reaction mixture was then filtered through Amberlite and evaporated. Flash chromatography (SiO_2, petrol/ether 97:3→9:1, *v*/*v*) afforded the *title compound* as a colourless oil (63 mg, 75%).

R_f 0.52 (ether/petrol, 2:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2937m, 1713m, 1631s, 1586m, 1486w, 1462w, 1377w, 1283w, 1249m, 1128s, 1047s, 837w, 692m; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.21 (m, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.84–6.76 (m, 2H), 4.75 (s, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 2.92 (q, *J* = 7.5 Hz, 2H), 2.34 (s, 3H), 1.27 (t, *J* = 7.5 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.8, 167.5, 153.5, 140.3, 129.7, 126.4, 122.2, 118.5, 95.0, 59.5, 25.0, 21.4, 14.4, 12.0; MS (ESI^+) *m*/*z* (rel. %) 257 ($[M+Na]^+$, 30), 235 ($[M+H]^+$, 100); HRMS (ESI^+) 235.1330 $[M+H]^+$, $C_{14}H_{19}O_3$ requires 235.1329.

Lab book reference number: TOR-1-47

(*E*)-3-(3-Methylphenoxy)pent-2-enoic acid (340)

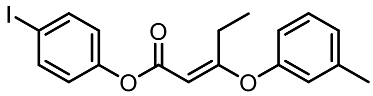


A solution of ester **116** (87 mg, 0.37 mmol), LiBr (321 mg, 3.70 mmol) and triethylamine (153 µL, 1.11 mmol) in MeCN (1 mL) and water (20 µL) was stirred at RT for 6 h, then heated to reflux for 3.5 days. After this time, water (5 mL) was added, the aqueous solution acidified to pH 2, and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (10 mL), dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 9:1→ether, *v*/*v*) afforded the *title compound* as a white solid (34 mg, 45%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.22 (m, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.91–6.66 (m, 2H), 4.78 (s, 1H), 2.93 (q, *J* = 7.5 Hz, 2H), 2.36 (s, 3H), 1.28 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 173.1, 153.4, 140.4, 129.8, 126.7, 122.1, 118.5, 94.5, 25.4, 21.4, 12.0; MS (ESI^+) *m*/*z* (rel. %) 229 ($[M+Na]^+$, 50), 207 ($[M+H]^+$, 100); HRMS (ESI^+) 207.1024 $[M+H]^+$, $C_{12}H_{15}O_3$ requires 207.1016.

Lab book reference number: TOR-2-108

4-Iodophenyl (*E*)-3-(3-methylphenoxy)pent-2-enoate (135)



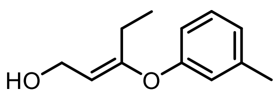
4-Iodophenol (27.5 mg, 0.13 mmol) was added to a solution of acid **338** (23.4 mg, 0.11 mmol), DCC (25.8 mg, 0.13 mmol) and DMAP (1.4 mg, 0.01 mmol) in dry CH_2Cl_2 (2 mL), and the reaction stirred for 22 h at RT. The resulting suspension was filtered, and the filtrate concentrated *in vacuo*. Flash chromatography (SiO_2, petrol/ether, 19:1, *v*/*v*) afforded the *title compound* as a white solid (39 mg, 85%). Single crystals were grown by slow evaporation from MeOH in a small vial.

M.P. 100–102 °C; R_f 0.49 (ether/petrol, 1:9, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2926w, 1732m, 1626s, 1582m, 1481s, 1380w, 1247m, 1206s, 1167w, 1145w, 1108s, 991m, 806w, 693w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.61 (m, 2H), 7.31 (td, *J* = 7.5, 1.0 Hz, 1H), 7.10–7.05 (m, 1H), 6.90–6.84 (m, 2H), 6.84–6.80 (m, 2H), 4.95 (s, 1H), 2.96 (q, *J* = 7.5 Hz, 2H), 2.39 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.7, 165.6, 153.3, 150.8, 140.6, 138.4, 129.9, 126.9, 124.2, 122.1, 118.5, 93.6, 89.4, 25.4, 21.5, 11.9; MS (ESI$^+$) *m/z* (rel. %) 431 ([M+Na]$^+$, 30), 409 ([M+H]$^+$, 100); HRMS (ESI$^+$) 409.0305 [M+H]$^+$, $C_{18}H_{18}IO_3$ requires 409.0295.

For X-ray crystallographic data, see Appendix 3.

Lab book reference number: TOR-2-112

(*E*)-3-(3-methylphenoxy)pent-2-en-1-ol (136)



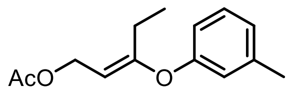
Diisobutylaluminium hydride (1.0 M in hexanes, 3.47 mL, 3.47 mmol) was added to a solution of ester **116** (407 mg, 1.74 mmol) in dry ether (15 mL) at −78 °C. After stirring for 2 h, the reaction mixture was poured onto a vigorously stirred mixture of ether (100 mL) and 0.5 M aq. Rochelle's salt (100 mL) and stirred for a further 1.5 h. The layers were separated, and the aqueous layer extracted with ether (3 × 60 mL). The combined organics were then dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 4:1→3:7, *v*/*v*) afforded the *title compound* as a colourless oil (283 mg, 85%).

R_f 0.39 (EtOAc/petrol, 1:1, *v*/*v*); IR ($CHCl_3$, cm^{-1}) ν_{max} 3342br, 2978m, 2936m, 2879m, 1667m, 1610m, 1587m, 1486s, 1377w, 1255s, 1168s, 1054m, 984s, 798m, 781m; ^{1}H NMR

(400 MHz, C_6D_6) δ 7.04 (t, J = 7.7 Hz, 1H), 6.90–6.83 (m, 2H), 6.78–6.73 (m, 1H), 4.84 (t, J = 7.7 Hz, 1H), 3.85 (d, J = 7.7 Hz, 2H), 2.22 (q, J = 7.5 Hz, 2H), 2.05 (s, 3H), 1.12 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 161.3, 156.1, 139.9, 129.7, 128.4, 124.8, 121.6, 118.0, 105.6, 58.4, 20.1, 21.3; MS (ESI$^+$) m/z (rel. %) 215 ([M+Na]$^+$, 45), 175 ([M+H−H_2O]$^+$, 100); HRMS (ESI$^+$) 215. 1037 [M+Na]$^+$, $C_{12}H_{16}NaO_2$ requires 215.1043.

Lab book reference number: TOR-3-194

(*E*)-3-(3-Methylphenoxy)pent-2-enyl acetate (137)

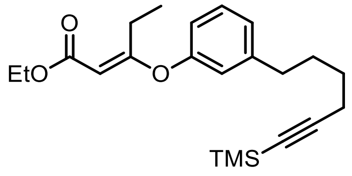


Acetic anhydride (540 µL, 584 mg, 5.72 mmol) was added to a solution of alcohol **136** (550 mg, 2.86 mmol), triethylamine (558 µL, 4.0 mmol) and DMAP (49 mg, 0.40 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The resulting solution was stirred at RT for 2.5 h before being quenched with sat. aq. NH_4Cl (20 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 95:5, v/v) afforded the *title compound* as a colourless oil (630 mg, 94%).

R_f 0.51 (ether/petrol, 2:3, v/v); IR (thin film, cm^{-1}) ν_{max} 2975w, 1738s, 1666m, 1486m, 1365m, 1230s, 1182s, 1152m, 1055w, 1020m; ^{1}H NMR (400 MHz, C_6D_6) δ 7.03–6.97 (m, 1H), 6.85–6.80 (m, 2H), 6.74–6.70 (m, 1H), 4.82 (t, J = 8.1 Hz, 1H), 4.52 (d, J = 8.1 Hz, 2H), 2.30 (q, J = 7.5 Hz, 2H), 2.01 (s, 3H), 1.62 (s, 3H), 1.14 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.1, 164.0, 155.5, 140.0, 129.7, 125.2, 121.9, 118.3, 88.6, 60.6, 23.3, 21.2, 20.6, 12.6; MS (ESI$^+$) m/z (rel. %) 257 ([M+Na]$^+$, 90), 197 ([M+Na−AcOH]$^+$, 15), 175 ([M+H−AcOH]$^+$, 100); HRMS (ESI$^+$) 257.1143 [M+Na]$^+$, $C_{14}H_{18}NaO_3$ requires 257.1148.

Lab book reference number: TOR-3-272

Ethyl (*E*)-3-(3-[6-trimethylsilyl-5-hexynyl]phenoxy)pent-2-enoate (139)

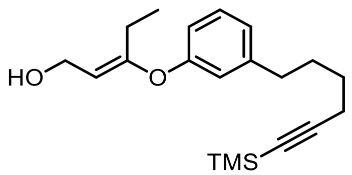


A flame-dried Schlenk tube containing a stirrer bar was charged with K_3PO_4 (1.09 g, 5.12 mmol) before being evacuated and backfilled with nitrogen. Dry toluene (5 mL) was added, followed by a solution of phenol **101** (756 mg, 3.07 mmol) in dry toluene (5 mL), a pre-mixed solution of $Pd(OAc)_2$ (14.4 mg, 0.06 mmol) and X-Phos (61 mg, 0.13 mmol) in dry toluene (5 mL), and a solution of triflate (*E*)**-134** (711 mg, 2.56 mmol) in dry toluene (5 mL). The resulting mixture was heated to 100 °C for 2 h, before being cooled to RT, filtered through Celite and evaporated. Flash chromatography (SiO_2, petrol/ether 95:5→85:15, *v*/*v*) afforded the *title compound* as a colourless oil (579 mg, 61%).

R_f 0.58 (EtOAc/petrol, 1:4, *v*/*v*); IR ($CHCl_3$, cm^{-1}) ν_{max} 2961m, 2948m, 2173m, 1712s, 1632s, 1584m, 1485m, 1444w, 1378m, 1283w, 1247s, 1222m, 1129s, 1046s, 1000w, 841s, 760m, 697m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.25 (m, 1H), 7.04 (ddd, *J* = 7.7, 1.7, 1.1 Hz, 1H), 6.82 (ddd, *J* = 3.9, 2.3, 0.9 Hz, 2H), 4.77 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.94 (q, *J* = 7.5 Hz, 2H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.26 (t, *J* = 7.1 Hz, 2H), 1.83–1.65 (m, 2H), 1.61–1.50 (m, 2H), 1.28 (t, *J* = 7.5 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 167.6, 153.7, 144.9, 129.8, 125.8, 121.5, 119.0, 107.3, 95.1, 84.9, 59.6, 35.2, 30.3, 28.1, 25.1, 19.8, 14.5, 12.0, 0.3; MS (ESI$^+$) *m*/*z* (rel. %) 395 ([M+Na]$^+$, 100), 373 ([M+H]$^+$, 80); HRMS (ESI$^+$) 373.2176 [M+H]$^+$, $C_{22}H_{33}O_3Si$ requires 373.2193.

Lab book reference number: TOR-5-414

(*E*)-3-(3-[6-Trimethylsilyl-5-hexynyl]phenoxy)pent-2-en-1-ol (341)

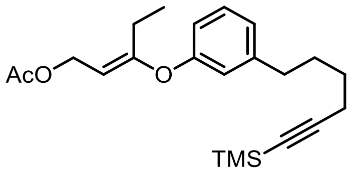


Diisobutylaluminium hydride (1.0 M in hexanes, 0.68 mL, 0.68 mmol) was added to a solution of ester **139** (126 mg, 0.34 mmol) in dry ether (6 mL) at −78 °C. After stirring for 2 h, the reaction mixture was poured onto a vigorously stirred mixture of ether (35 mL) and 0.5 M aq. Rochelle's salt (35 mL) and stirred for a further 20 h. The layers were separated, and the aqueous layer extracted with ether (3 × 25 mL). The combined organics were then dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 4:1, *v*/*v*) afforded the *title compound* as a colourless oil (93 mg, 95%).

R_f 0.34 (ether/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3331br, 2937m, 2860w, 2173m, 1667m, 1606m, 1586m, 1485m, 1445m, 1248s, 1169m, 1054m, 986m, 840s, 759s, 697m, 639m; ^{1}H NMR (400 MHz, C_6D_6) δ 7.07 (t, *J* = 7.8 Hz, 1H), 6.93–6.83 (m, 2H), 6.76 (dt, *J* = 7.7, 1.2 Hz, 1H), 4.84 (t, *J* = 7.7 Hz, 1H), 3.86 (d, *J* = 7.5 Hz, 2H), 2.33 (dd, *J* = 8.6, 6.7 Hz, 2H), 2.23 (q, *J* = 7.4 Hz, 2H), 2.01 (t, *J* = 7.1 Hz, 2H), 1.58–1.46 (m, 2H), 1.38–1.29 (m, 2H), 1.13 (t, *J* = 7.5 Hz, 3H), 0.22 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 161.3, 156.1, 144.5, 129.7, 124.1, 121.0, 118.3, 107.7, 105.6, 84.4, 58.4, 35.4, 30.6, 28.3, 23.1, 20.0, 12.8, 0.37; MS (ESI$^+$) *m/z* (rel. %) 353 ([M+Na]$^+$, 95), 313 ([M+H−H_2O]$^+$, 100); HRMS (ESI$^+$) 353.1893 [M+Na]$^+$, $C_{20}H_{20}NaO_2Si$ requires 353.1907.

Lab book reference number: TOR-1-88

(*E*)-3-(3-[6-Trimethylsilyl-5-hexynyl]phenoxy)pent-2-enyl acetate (140)

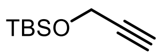


Acetic anhydride (60 µL, 65 mg, 0.64 mmol) was added to a solution of crude alcohol **339** (0.32 mmol), triethylamine (58 µL, 0.45 mmol) and DMAP (5.5 mg, 0.04 mmol) in CH_2Cl_2 (5 mL) at RT. The resulting solution was stirred at RT for 2 h before being quenched with sat. aq. NH_4Cl (10 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 85:15, *v*/*v*) afforded the *title compound* as a colourless oil (111 mg, 93% over two steps).

R_f 0.52 (EtOAc/petrol, 1:4, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2939w, 2174w, 1739m, 1664w, 1585w, 1484w, 1444w, 1365w, 1247s, 1227s, 1181m, 1020m, 946w, 841s, 760w, 697w; ^{1}H NMR (400 MHz, C_6D_6) δ 7.03 (t, *J* = 7.7 Hz, 1H), 6.82–6.87 (m, 2H), 6.73 (dtt, *J* = 7.6, 1.1, 0.5 Hz, 1H), 4.83 (t, *J* = 8.1 Hz, 1H), 4.52 (d, *J* = 8.1 Hz, 2H), 2.23–2.35 (m, 4H), 2.01 (t, *J* = 7.1 Hz, 2H), 1.64 (s, 3H), 1.54–1.44 (m, 2H), 1.36–1.27 (m, 2H), 1.15 (t, *J* = 7.5 Hz, 3H), 0.22 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.1, 164.0, 155.6, 144.6, 129.8, 124.5, 121.2, 118.5, 107.7, 99.7, 84.8, 60.6, 35.3, 30.5, 28.3, 23.3, 20.6, 19.9, 12.7, 0.4; MS (ESI$^+$) *m*/*z* (rel. %) 395 ([M+Na]$^+$, 100), 335 ([M+Na−AcOH]$^+$, 20), 313 ([M−OAc]$^+$, 50); HRMS (ESI$^+$) 395.2001 [M+Na]$^+$, $C_{22}H_{32}NaO_3Si$ requires 395.2013.

Lab book reference number: TOR-5-445, TOR-5-446

1-(*tert*-Butyldimethylsilyloxy)-2-propyne (106)[273]



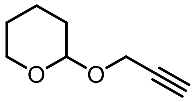
A solution of propargyl alcohol (3.0 g, 53.5 mmol), *tert*-butyldimethylchlorosilane (12.1 g, 80.3 mmol) and imidazole (5.4 g, 80.3 mmol) in dry CH_2Cl_2 (150 mL) was stirred for 2.5 h at RT. The reaction was quenched with sat. aq. NH_4Cl (100 mL), and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine

(100 mL), dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 19:1, *v*/*v*) afforded the *title compound* as a colourless oil (8.98 g, 100%).

R_f 0.64 (ether/petrol, 1:9, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3312w, 2956m, 2930m, 2887w, 2859m, 2182w, 1473w, 1254m, 1091s, 1004w, 922w, 832s, 776s, 725w, 659m, 625m 537w; ^1H NMR (400 MHz, $CDCl_3$) δ 4.31 (d, J = 2.4 Hz, 2H), 2.39 (t, J = 2.4 Hz, 1H), 0.91 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.6, 73.0, 51.7, 25.9, 18.4, −5.1.

Lab book reference number: TOR-1-80

2-(2-Propynyloxy)tetrahydro-2*H*-pyran (141)[274]

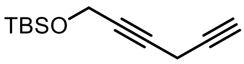


3,4-Dihydro-2*H*-pyran (1.65 g, 19.6 mmol) was added dropwise to a solution of propargyl alcohol (1.0 g, 17.8 mmol) and *p*-toluenesulfonic acid (34 mg, 0.18 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. The resulting solution was stirred at RT for 3 h before being diluted with CH_2Cl_2 (20 mL). The reaction mixture was washed with sat. aq. $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL) then dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 19:1, *v*/*v*) afforded the *title compound* as a colourless oil (2.21 g, 90%).

R_f 0.31 (ether/petrol, 1:9, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3290w, 2943m, 2871w, 1442w, 1346w, 1201m, 1119s, 1057m, 1024s, 948m, 901m, 870m, 815m, 662m, 570w; ^1H NMR (400 MHz, $CDCl_3$) δ 4.82 (t, J = 3.4 Hz, 1H), 4.30 (dd, J = 15.7, 2.5 Hz, 1H), 4.23 (dd, J = 15.7, 2.5 Hz, 1H), 3.89–3.80 (m, 1H), 3.58–3.50 (m, 1H), 2.41 (t, J = 2.4 Hz, 1H), 1.90–1.69 (m, 2H), 1.69–1.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 97.0, 79.9, 74.1, 62.1, 54.1, 30.4, 25.5, 19.1.

Lab book reference number: TOR-2-106

1-(*tert*-Butyldimethylsilyloxy)-2,5-hexadiyne (107)

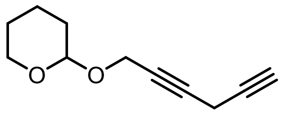


Magnesium turnings (92 mg, 3.81 mmol) were added to a Schlenk tube, which was then evacuated and backfilled with nitrogen. A small crystal of iodine was added, followed by dry THF (6 mL). A solution of ethyl bromide (263 µL, 3.52 mmol) in dry THF (2 mL) was added dropwise, and the resulting mixture stirred at 50 °C for 45 min, before a solution of alkyne **106** (500 mg, 2.94 mmol) in dry THF (2 mL) was added. The reaction mixture was stirred for a further 1 h at 50 °C. Heating was removed and the reaction cooled to RT before CuCl (8.9 mg, 0.09 mmol) was added. The reaction was then heated to 50 °C and stirred for 15 min before propargyl bromide (80% in toluene, 328 µL, 2.94 mmol) was added dropwise. The reaction mixture was stirred for a further 45 min at 50 °C, cooled to RT and quenched with sat. aq. NH_4Cl (7 mL). The layers were separated and the aqueous layer extracted with hexane (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol→petrol/ether, 99:1, *v*/*v*) afforded the *title compound* as a colourless oil which rapidly turned yellow in air (119 mg, 20%).

R_f 0.52 (ether/petrol, 1:9, *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (t, J = 2.2 Hz, 2H), 3.20 (q, J = 2.4 Hz, 2H), 2.06 (t, J = 2.7 Hz, 1H), 0.91 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.6, 78.3, 78.0, 69.0, 52.0, 26.0, 18.5, 9.9, −5.0.

Lab book reference number: TOR-1-84

2-(2,5-Hexadiynyloxy)tetrahydro-2*H*-pyran (142)[275]

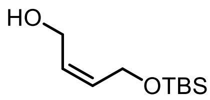


Magnesium turnings (226 mg, 9.28 mmol) were added to a Schlenk tube, which was then evacuated and backfilled with nitrogen. Dry THF (15 mL) was added, followed by ethyl bromide (263 µL, 3.52 mmol), and the resulting mixture stirred at 50 °C for 45 min, before a solution of alkyne **141** (885 mg, 6.31 mmol) in dry THF (5 mL) was added. The reaction mixture was stirred for a further 1 h at 50 °C. Heating was removed and the reaction cooled to RT before CuCl (8.9 mg, 0.09 mmol) was added, the reaction stirred for 15 min, and propargyl bromide (80% in toluene, 360 µL, 3.23 mmol) added dropwise. The reaction mixture was stirred for a further 2 h at 50 °C, cooled to RT and quenched with sat. aq. NH_4Cl (15 mL). The layers were separated and the aqueous layer extracted with hexane (3 × 40 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 19:1, *v*/*v*) afforded the *title compound* as a colourless oil which rapidly turned yellow in air (704 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (t, J = 3.4 Hz, 1H), 4.30 (dt, J = 15.4, 2.2 Hz, 1H), 4.20 (dt, J = 15.4, 2.2 Hz, 1H), 3.91–3.75 (m, 1H), 3.62–3.44 (m, 1H), 3.22 (dt, J = 2.9, 2.2 Hz, 2H), 2.07 (t, *J* = 2.7 Hz, 1H), 1.91–1.68 (m, 2H), 1.65–1.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 97.0, 79.5, 78.0, 77.0, 69.1, 62.1, 54.5, 30.4, 25.5, 19.2, 9.9.

Lab book reference number: TOR-2-119

(*Z*)- 4-(*tert*-Butyldimethylsilyloxy)but-2-en-1-ol (149)[276]

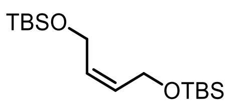


A solution of *tert*-butyldimethylsilylchloride (1.71 g, 11.3 mmol) in dry CH_2Cl_2 (6 mL) was added dropwise to a solution of *cis*-2-butene-1,4-diol (1.0 g, 11.3 mmol) and dry triethylamine (1.80 mL, 13.6 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C *via* syringe pump over 45 min. After stirring for an additional 30 min, the reaction mixture was quenched with water (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 15 mL), washed with water (20 mL), dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 7:3, *v*/*v*) afforded the *title compound* as a colourless oil (1.67 g, 73%).

^{1}H NMR (400 MHz, acetone-d_6) *δ* 5.64–5.51 (m, 1H), 5.58–5.45 (m, 1H), 4.31–4.22 (m, 2H), 4.19–4.08 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, acetone-d_6) *δ* 131.6, 131.0, 60.0, 58.6, 26.3, 18.8, −5.1; MS (ESI$^+$) *m*/*z* (rel. %) 225 ([M+Na]$^+$, 35), 203 ([M+H]$^+$, 100), 185 ([M−H_2O+H]$^+$, 45); HRMS (ESI$^+$) 203.1461 [M+H]$^+$, $C_{10}H_{23}O_2Si$ requires 203.1462.

Lab book reference number: TOR-2-131

(*Z*)-1,4-Di(*tert*-butyldimethylsilyloxy)but-2-ene (342)[277]

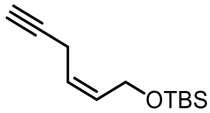


Title compound isolated as a side product from the synthesis of **149** (408 mg, 11%).

R_f 0.81 (ether/petrol, 2:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2955m, 2929m, 2857m, 1472w, 1361w, 1254s, 1078s, 1006m, 939w, 833s, 773s, 668w; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.62–5.47 (m, 2H), 4.23 (dt, *J* = 3.2, 0.9 Hz, 4H), 0.90 (s, 18H), 0.07 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 130.3, 59.8, 26.1, 18.5, −5.0; MS (ESI$^+$) *m*/*z* (rel. %) 339 ([M+Na]$^+$, 25), 317 ([M+H]$^+$, 100); HRMS (ESI$^+$) 317.2321 [M+H]$^+$, $C_{16}H_{37}O_2Si_2$ requires 317.2327.

Lab book reference number: TOR-2-131

(*Z*)-6-(*tert*-Butyldimethylsilyloxy)hex-4-en-1-yne (147)



METHOD A: To a mixture of alcohol **149** (1.02 g, 5.06 mmol) and dry triethylamine (1.53 g, 15.2 mmol) in dry THF (20 mL) at 0 °C was added methanesulfonyl chloride (1.16 g, 10.1 mmol) dropwise. After stirring for 1 h at RT, the reaction mixture was diluted with ether (40 mL), washed with sat. aq. NH_4Cl (2 × 20 mL) and brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude mesylate as a yellow oil, which was used in the next step without further purification.

To a solution of ethynylmagnesium bromide (0.5 M in THF, 40.5 mL, 20.2 mmol) at 0 °C in a Schlenk tube was added CuI (674 mg, 3.54 mmol) followed by a solution of the crude mesylate in dry THF (6 mL). The reaction mixture was heated to 60 °C for 19 h before being cooled to RT and quenched with sat. aq. NH_4Cl (20 mL). The layers were separated, and the aqueous extracted with ether (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether 19:1, *v*/*v*) afforded the *title compound* as a colourless oil (341 mg, 32%).

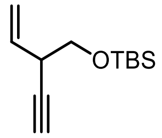
METHOD B: To a rapidly stirred suspension of phosphonium salt **162** (4.84 g, 12.1 mmol) in dry THF (47 mL) at −78 °C was added dropwise *n*-butyllithium (2.5 M in hexanes, 4.6 mL, 11.6 mmol). After stirring for 5 min at −78 °C, the solution was warmed to 0 °C for 1.5 h, before being cooled once again to −78 °C, and a solution of aldehyde **163** (1.75 g, 10.0 mmol) in dry THF (14 mL) was added dropwise *via* syringe. Transfer was made quantitative with an additional portion of dry THF (14 mL). The reaction mixture was allowed to warm to RT over 2 h. After a further 14 h at RT, the reaction was quenched with sat. aq. NH_4Cl (80 mL), and the aqueous later extracted with ether (3 × 130 mL). The combined organic layers were washed with brine (130 mL), dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 98:2, *v*/*v*) afforded the *title compound* as a pale yellow oil (2.03 g, 96%).

R_f 0.76 (ether/petrol, 2:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3312w, 2930m, 2954m, 2858m, 1472w, 1464w, 1258s, 1091s, 1017s, 939w, 835s, 798s, 779s, 667m, 638m; ^1H NMR (400 MHz, $CDCl_3$) δ 5.62 (dtt, *J* = 10.6, 5.9, 1.6 Hz, 1H), 5.49 (dtt, *J* = 10.6, 7.0, 1.6 Hz, 1H), 4.25 (ddd, *J* = 5.9, 1.6, 0.9 Hz, 2H), 2.98 (dtd, *J* = 7.0, 1.6, 0.9 Hz, 2H), 1.98 (t, *J* = 2.7 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.8, 124.6, 82.3, 68.5, 59.4, 26.1, 18.5, 17.4, −5.1; MS (ESI$^+$) *m/z* (rel. %) 233 ([M+Na]$^+$, 30), 211 ([M+H]$^+$, 100); HRMS (ESI$^+$) 211.1511 [M+H]$^+$, $C_{12}H_{23}O$ requires 211.1513.

Lab book reference numbers (method A): TOR-2-125, TOR-2-126

Lab book reference number (method B): TOR-4-307

3-([*tert*-Butyldimethylsilyloxy]methyl)pent-4-en-1-yne (150)

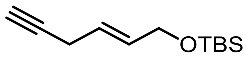


Title compound was isolated as a side product from the synthesis of **147** by method A (146 mg, 14%)

R_f 0.78 (ether/petrol, 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddd, J = 17.1, 10.2, 5.8 Hz, 1H), 5.39 (dt, J = 17.1, 1.6 Hz, 1H), 5.18 (dt, J = 10.2, 1.6 Hz, 1H), 3.73 (dd, J = 9.5, 6.3 Hz, 1H), 3.59 (dd, J = 9.5, 7.6 Hz, 1H), 3.23 (qdd, J = 6.1, 2.4, 1.4 Hz, 1H), 2.21 (d, J = 2.4 Hz, 1H), 0.89 (s, 9H), 0.06 (d, J = 1.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 116.9, 82.7, 72.1, 66.4, 38.7, 25.9, 18.4, −5.2.

Lab book reference number: TOR-2-125, TOR-2-126

(*E*)-6-(*tert*-Butyldimethylsilyloxy)hex-4-en-1-yne (152)



To a mixture of alcohol **149** (1.67 g, 8.25 mmol) and dry triethylamine (2.51 g, 24.8 mmol) in dry THF (30 mL) at 0 °C was added methanesulfonyl chloride (1.89 g, 16.5 mmol) dropwise. After stirring for 1 h at RT, the reaction mixture was diluted with ether (60 mL), washed with sat. aq. NH_4Cl (2 × 30 mL) and brine (2 × 30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude mesylate as a yellow oil, which was used in the next step without further purification.

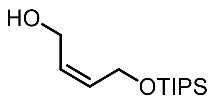
To a solution of the crude mesylate in acetone (5 mL) at 0 °C was added NaI (680 mg, 4.54 mmol), and the resulting suspension stirred at RT for 1 h. After this time the reaction mixture was diluted with water (5 mL) and the acetone removed *in vacuo*. The resulting aqueous solution was extracted with ether (3 × 20 mL), and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated to afford a clear oil which was used in the next step without purification.

To a solution of ethynylmagnesium bromide (0.5 M in THF, 16.5 mL, 8.24 mmol) at 0 °C in a Schlenk tube was added CuI (275 mg, 1.44 mmol) followed by a solution of the crude iodide in dry THF (4 mL). The reaction mixture was heated to 60 °C for 19 h before being cooled to RT and quenched with sat. aq. NH_4Cl (10 mL). The layers were separated, and the aqueous lyaer extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 98:2, *v*/*v*) afforded the *title compound* as a colourless oil (357 mg, 83%, *E*/*Z* 10:1).

R_f 0.57 (ether/petrol, 1:9, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3314w, 2956m, 2930m, 2857m, 1472w, 1379w, 1256m, 1119m, 1084m, 1048m, 969m, 834s, 812m, 775s, 631s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dtt, J = 15.2, 4.8, 1.7 Hz, 1H), 5.66 (dtt, J = 15.2, 5.5, 1.7 Hz, 1H), 4.17 (dq, J = 5.0, 1.7 Hz, 2H), 2.96 (ddq, J = 5.2, 2.6, 1.7 Hz, 2H), 2.10 (t, J = 2.6 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.4, 123.9, 81.7, 70.4, 63.4, 26.1, 21.5, 18.6, −5.1.

Lab book reference numbers: TOR-2-132, TOR-2-133, TOR-2-134

(*Z*)- 4-(Triisopropylsilyloxy)but-2-en-1-ol (156)[278]

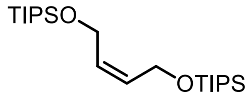


To a solution of *cis*-2-butene-1,4-diol (1.0 g, 11.3 mmol) and dry triethylamine (1.90 mL, 13.6 mmol) in dry CH_2Cl_2 (10 mL) was added triisopropylsilylchloride (2.43 mL, 11.3 mmol) dropwise *via* syringe pump over 1 h at 0 °C. After stirring for an additional 1 h, the reaction mixture was quenched with water (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL), washed with water (20 mL), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether 9:1→3:2, *v*/*v*) afforded the *title compound* as a colourless oil (1.71 g, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73–5.69 (m, 2H), 4.27–4.31 (m, 2H), 4.23–4.18 (m, 2H), 1.36–0.80 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.6, 130.0, 60.0, 59.2, 18.1, 12.1; MS (ESI$^+$) *m*/*z* (rel. %) 267 ($[M+Na]^+$, 100), 245 ($[M+H]^+$, 30); HRMS (ESI$^+$) 267.1751 $[M+Na]^+$, $C_{13}H_{28}NaO_2Si$ requires 267.1751.

Lab book reference number: TOR-2-156

(*Z*)-1,4-Di(triisopropylsilyloxy)but-2-ene (343)[279]

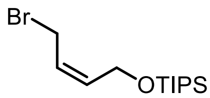


Title compound was isolated as a by-product from the synthesis of **156** (79 mg, 1.7%).

R_f 0.81 (ether/petrol, 2:3, *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (t, J = 3.1 Hz, 2H), 4.32–4.28 (m, 4H), 1.18–0.96 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.3, 60.1, 18.1, 12.1.

Lab book reference number: TOR-2-156

(*Z*)-1-Bromo-4-(triisopropylsilyloxy)but-2-ene (159)[280]

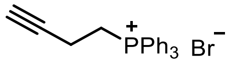


Triphenylphosphine (361 mg, 1.37 mmol) was added to a solution of carbon tetrabromide (438 mg, 1.32 mmol) and alcohol **156** (280 mg, 1.15 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C. The solution was stirred for 25 min before the solvent was evaporated, and hexane (75 mL) added. The resulting precipitate was filtered off and the filtrate evaporated. Flash chromatography (SiO_2, petrol/ether 98:2, *v*/*v*) afforded the *title compound* as a colourless oil (297 mg, 84%).

R_f 0.77 (ether/petrol, 2:3, *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80–5.66 (m, 2H), 4.40 (dd, J = 5.2, 1.2 Hz, 2H), 4.11–3.98 (m, 2H), 1.20–0.96 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 125.7, 59.5, 27.2, 18.1, 12.1; MS (ESI$^+$) *m*/*z* (rel. %) 329 ([M+Na]$^+$, 100), 307 ([M+H]$^+$, 10); HRMS (ESI$^+$) 329.0937 [M+Na]$^+$, $C_{13}H_{27}BrNaOSi$ requires 329.0907.

Lab book reference number: TOR-2-157

3-Butynyltriphenylphosphonium bromide (162)[281]

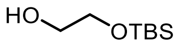


A solution of triphenylphosphine (recrystallised from hot ethanol and vacuum dried over P_2O_5, 8.9 g, 33.8 mmol) and 4-bromo-1-butyne (4.95 g, 37.2 mmol) in dry MeCN (35 mL) was stirred at 80 °C for 72 h. After being cooled to RT, the MeCN was removed *in vacuo*, and benzene (40 mL) was added. The resulting precipitate was filtered, washed with benzene and dried *in vacuo* to afford the *title compound* as a pale brown solid (13.0 g, 98%).

M.P. 167–169 °C (lit.[281] 152–154 °C); IR (ATR, cm^{-1}) ν_{max} 3190m, 2049w, 2889w, 2861w, 1587w, 1485w, 1436s, 1329w, 1214w, 1112s, 995m, 946m, 798m, 753m, 714s, 686s, 555s, 504s, 481s, 456s; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (ddq, J = 7.4, 6.6, 1.6 Hz, 3H), 7.87–7.74 (m, 12H), 3.98–3.84 (m, 2H), 3.01 (t, J = 2.6 Hz, 1H), 2.56 (dddd, J = 13.0, 7.5, 6.6, 2.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 135.1 (d, J = 3.0 Hz), 133.8 (d, J = 10.3 Hz), 130.3 (d, J = 12.6 Hz), 117.9 (d, J = 86.2), 81.1 (d, J = 17.5 Hz), 74.0 (d, J = 1.6 Hz), 19.8 (d, J = 50.6 Hz), 12.0 (d, J = 2.4 Hz); ^{31}P NMR (162 MHz, DMSO-d_6) δ 24.3; MS (ESI$^+$) m/z (rel. %) 315 ([M−Br]$^+$, 100); HRMS (ESI$^+$) 315.1298 [M−Br]$^+$, $C_{22}H_{20}P$ requires 315.1297.

Lab book reference number: TOR-3-205

2-(*Tert*-butyldimethylsilyloxy)ethanol (165)[141]

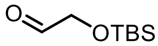


A solution of *tert*-butyldimethylsilylchloride (20.0 g, 133 mmol) in CH_2Cl_2 (20 mL) was added dropwise at 0 °C to a solution of ethane-1,2-diol (37 mL, 41.2 g, 663 mmol) and triethylamine (67 mL, 92.4 g, 663 mmol) in CH_2Cl_2 (250 mL) *via* syringe pump over a period of 2 h. The resulting solution was stirred at RT for a further 1.5 h and quenched with water (160 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 120 mL). The combined organic layers were washed with water (120 mL) and brine (120 mL), dried over $MgSO_4$, filtered and evaporated. The crude residue was purified by filtration through a short plug of silica using petrol/ether (1:1, *v*/*v*), affording the *title compound* as a colourless oil (22.2 g, 95%).

R_f 0.53 (EtOAc/petrol, 1:1, *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74–3.68 (m, 2H), 3.66–3.61 (m, 2H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.2, 63.8, 26.0, 18.5, −5.2; MS (ESI$^+$) m/z (rel. %) 199 ([M+Na]$^+$, 100), 179 ([M+H]$^+$, 50); HRMS (ESI$^+$) 199.1133 [M+Na]$^+$, $C_8H_{20}NaO_2Si$ requires 199.1125.

Lab book reference number: TOR-6-506

2-(*Tert*-butyldimethylsilyloxy)ethanol (163)[282]

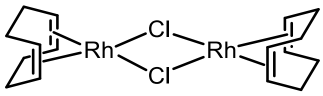


To a solution of oxalyl chloride (2.68 mL, 31.2 mmol) in dry CH_2Cl_2 (70 mL) was added a solution of dry DMSO (4.83 mL, 68 mmol) in dry CH_2Cl_2 (14 mL) dropwise *via* dropping funnel at −78 °C. After stirring for 10 min, a solution of alcohol **165** (5.0 g, 28.3 mmol) and dry pyridine (4.56 mL, 56.6 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise and the solution stirred for an additional 25 min. Dry triethylamine (19.8 mL, 142 mmol) was then added dropwise and the resulting suspension allowed gradually to warm to RT; 1 M aq. HCl was added until the aqueous layer was pH 5. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with sat. aq. $CuSO_4$ (50 mL), dried ($MgSO_4$), filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 9:1→85:15, *v*/*v*) afforded the *title compound* as a volatile colourless oil (4.93 g, 99%).

R_f 0.42 (ether/petrol, 2:3, *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (t, *J* = 0.9 Hz, 1H), 4.21 (d, *J* = 0.8 Hz, 2H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5, 69.8, 25.9, 18.5, −5.3.

Lab book reference number: TOR-3-200

Di-μ-chloro-bis(η^4-1,5-cyclooctadiene)-dirhodium(I) (344)[142]



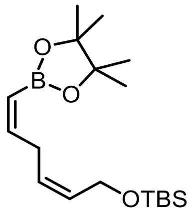
A three-necked, 25-mL round-bottomed flask was charged with $RhCl_3$ (491 mg, 1.87 mmol) and flushed with argon. Degassed ethanol/water (5:1, 6 mL) was then added, followed by 1,5-cyclooctadiene (0.75 mL), and the resulting solution was heated to reflux and stirred for 18 h before being allowed to cool. The resulting precipitate was filtered, washed with pentane and dried *in vacuo* to afford the *title compound* as a yellow-orange solid (387 mg, 84%).

M.P. 248 °C (dec.) (lit.[283] 256 °C (dec.)); IR (ATR, cm^{-1}) ν_{max} 2988w, 2935w, 2873m, 2827m, 1467m, 1423w, 1322m, 1299m, 1211w, 1172w, 1078w, 994s, 960s, 866m, 815s, 795m, 774m, 689w, 597w, 486s, 473s; ^{1}H NMR (400 MHz, C_6D_6) δ 4.29–4.16 (m, 8H), 2.50 (ddd, *J* = 7.6, 5.2, 2.1 Hz, 8H), 1.75 (q, *J* = 7.0 Hz, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.9, 78.8, 31.0; MS (LIFDI$^+$) *m*/*z* (rel. %) 492 ([M]$^+$, 100); HRMS (LIFDI$^+$) 491.9266

([M]$^+$), $C_{16}H_{24}Cl_2Rh_2$ requires 491.9365; Elemental anal.: C: 39.07, H: 4.87; $C_{16}H_{24}Cl_2Rh_2$ requires C: 38.97, H: 4.91.

Lab book reference number: TOR-3-225

2-[(1′Z,4′*Z*)-6′-(*Tert*-butyldimethylsilyloxy)hexa-1′,4′-dienyl]-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (166)

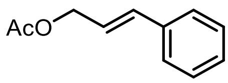


Pinacolborane (115 µL, 0.79 mmol) was added to a solution of $[Rh(cod)Cl]_2$ (**342**, 23.7 mg, 0.048 mmol), tricyclohexylphosphine (53 mg, 0.19 mmol) and dry triethylamine (0.55 mL, 3.95 mmol) in dry cyclohexane (10 mL) at RT. After 30 min, a solution of alkyne **147** (200 mg, 0.95 mmol) in dry cyclohexane (2 mL) was added and the reaction mixture stirred for 47 h. After this time, MeOH (1 mL) was added to quench any remaining borane and the solvent was removed *in vacuo*. Flash chromatography (SiO_2, petrol/ether, 95:5, *v*/*v*) afforded the *title compound* as a pale yellow oil (125 mg, 47%).

R_f 0.55 (ether/petrol, 1:9, *v*/*v*); IR ($CHCl_3$, cm^{-1}) ν_{max} 2978m, 2953s, 2931s, 2855m, 1627m, 1471w, 1422m, 1371w, 1325s, 1259s, 1145s, 1099s, 1075s, 836s, 776s; ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 (dt, J = 13.7, 7.4 Hz, 1H), 5.55 (dtt, J = 10.8, 5.9, 1.4 Hz, 1H), 5.44 (dtt, J = 10.8, 7.5, 1.5 Hz, 1H), 5.35 (dt, J = 13.7, 1.5 Hz, 1H), 4.29 (dtt, J = 6.1, 1.6, 0.7 Hz, 2H), 3.25–3.10 (m, 2H), 1.27 (s, 12H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 130.6, 128.2, 83.1, 59.7, 31.4, 26.1, 25.0, 18.5, −4.9 (C–B not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 28.9; MS (ESI$^+$) *m*/*z* (rel. %) 339 ([M+H]$^+$, 100), 361 ([M+Na]$^+$, 95); HRMS (ESI$^+$) 339.2525 [M+H]$^+$, $C_{18}H_{36}BO_3Si$ requires 339.2525.

Lab book reference number: TOR-3-217

Cinnamyl acetate (169)[284]

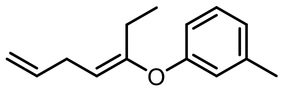


To a solution of cinnamyl alcohol (1.0 g, 7.45 mmol), triethylamine (1.45 mL, 10.4 mmol) and DMAP (127 mg, 1.04 mmol) in CH_2Cl_2 (30 mL) was added acetic anhydride (1.41 mL, 14.9 mmol) at 0 °C. The resulting solution was stirred at RT for 2.5 h, before being filtered through a short plug of silica, eluting with ether. The filtrate was evaporated to afford the *title compound* as a yellow oil (1.25 g, 95%).

IR (thin film, cm^{-1}) ν_{max} 3028w, 1733s, 1495w, 1449w, 1380m, 1362m, 1222s, 1068w, 1023s, 963s, 744s, 692s, 603m, 467w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.37 (m, 2H), 7.35–7.30 (m, 2H), 7.29–7.23 (m, 1H), 6.66 (dt, J = 15.8, 1.4 Hz, 1H), 6.29 (dt, J = 15.8, 6.5 Hz, 1H), 4.73 (dd, J = 6.5, 1.4 Hz, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 136.3, 134.4, 128.8, 128.2, 126.8, 123.3, 65.2, 21.2.

Lab book reference number: TOR-3-216

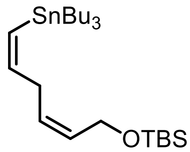
(*E*)-5-(3-Methylphenoxy)hepta-1,4-diene (177)



Tributyl(vinyl)tin (78 mg, 0.25 mmol) was added to a Schlenk tube containing a solution of acetate **137** (48 mg, 0.21 mmol), *cis*- or *trans*-Pd(*N*-succ)Br(PPh_3)$_2$ **23** (5.0 mg, 6.2 μmol) and LiCl (26 mg, 0.62 mmol) in dry DMF (1.5 mL) under N_2. The reaction mixture was then exposed to air for 5 seconds before being sealed and stirred for 24 h at RT. After this time, the reaction mixture was diluted with ether (20 mL), washed with water (3 × 10 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. A sample was purified in order to obtain analytical data.

R_f 0.44 (ether/petrol, 1:4, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2976m, 1669w, 1610m, 1587m, 1486s, 1464m, 1255s, 1154s, 1047m; ^{1}H NMR (400 MHz, C_6D_6) δ 7.05 (t, J = 7.7 Hz, 1H), 6.95–6.89 (m, 2H), 6.72 (ddt, J = 7.5, 1.7, 0.8 Hz, 1H), 5.69 (ddt, J = 17.1, 10.1, 6.0 Hz, 1H), 5.02 (dq, J = 17.1, 1.8 Hz, 1H), 4.93 (dq, J = 10.1, 1.6 Hz, 1H), 4.87 (t, J = 7.8 Hz, 1H), 2.59 (ddt, J = 7.7, 6.0, 1.7 Hz, 2H), 2.20 (q, J = 7.5 Hz, 2H), 2.06 (d, J = 0.8 Hz, 3H), 1.12 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 157.7, 157.0, 139.8, 137.6, 129.6, 124.0, 120.6, 116.8, 114.5, 105.8, 30.9, 22.6, 21.3, 12.4; MS (ESI^{+}) m/z (rel. %) 203 ([M+H], 100); HRMS (ESI^{+}) 203.1437, $C_{14}H_{19}O$ requires 203.1430.

(1*Z*,4*Z*)-1-Tri-*n*-butylstannyl-6-(*tert*-butyldimethylsilyloxy)hexa-1,4-diene (178)



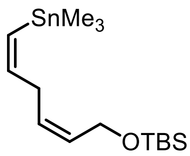
To a solution of alkyne **147** (485 mg, 2.31 mmol) in dry THF (18 mL) at −78 °C was added dropwise *n*-butyllithium (2.2 M in hexanes, 1.08 mL, 2.36 mmol), and the resulting solution was stirred for 10 min before dropwise addition of tributyltin chloride (826 mg, 2.54 mmol). The cooling bath was removed and the reaction mixture was stirred for a further 2 h, after which time it was diluted with ether (100 mL), washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and evaporated to afford a yellow oil which was used directly without further purification.

Diisobutylaluminium hydride (1.0 M in hexane, 3.47 mL, 3.47 mmol) was added dropwise to a solution of zirconocene dichloride (1.08 g, 3.69 mmol) in dry THF (15 mL) at 0 °C. The reaction mixture was then stirred for 30 min at 0 °C during which time an off-white suspension formed. A solution of the crude intermediate stannane was then added in dry THF (2 mL), with additional dry THF (2 mL) used to rinse the flask and ensure quantitative transfer. The cooling was then removed, and the reaction mixture rapidly became a homogenous red solution. After stirring for 1 h at RT, the reaction was diluted with *n*-pentane (20 mL) and quenched with water (3 eq., 125 µL), leading to the disappearance of the red colour and formation of a yellow precipitate. After stirring for 20 min, the reaction mixture was filtered through a Celite plug, which was washed copiously with hexane. Evaporation of the filtrate and flash chromatography (SiO_2, petrol/ether/triethylamine, 94:5:1, *v*/*v*) afforded the *title compound* as a colourless oil (767 mg, 66%).

R_f 0.73 (ether/petrol, 1:9, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2957s, 2927s, 2856m, 1595w, 1464m, 1253m, 1099s, 837s, 776m, 667w; ^{1}H NMR (400 MHz, C_6D_6) δ 6.58 (dt, J = 12.3, 7.0 Hz, $^3J_{^{119}Sn-H}$ = 141.6 Hz, $^3J_{^{117}Sn-H}$ = 135.2 Hz, 1H), 6.04 (dt, J = 12.3, 1.3 Hz, $^2J_{^{119}Sn-H}$ = 71.3 Hz, $^2J_{^{117}Sn-H}$ = 68.7 Hz, 1H), 5.73 (dtt, J = 10.9, 6.1, 1.7 Hz, 1H), 5.51 (dtt, J = 10.8, 7.3, 1.7 Hz, 1H), 4.31 (dtt, J = 6.2, 1.6, 0.8 Hz, 2H), 2.94 (t, J = 6.9 Hz, 2H), 1.61 (m, 6H), 1.4 (m, 6H), 1.03 (m, 6H), 1.00 (s, 9H), 0.95 (t, J = 7.3 Hz, 9H), 0.10 (s, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 147.0, 131.0, 129.2, 128.6, 59.7, 35.9, 29.7 ($^3J_{Sn-C}$ = 20.7 Hz), 27.8 ($^2J_{^{119}Sn-C}$ = 56.1 Hz, $^2J_{^{117}Sn-C}$ = 54.1 Hz), 26.2, 18.5, 14.0, 10.6 ($^1J_{^{119}Sn-C}$ = 338.9 Hz, $^1J_{^{117}Sn-C}$ = 322.8 Hz), −4.9; ^{119}Sn NMR (187 MHz, C_6D_6) δ −60.6; HRMS (ESI$^+$) 525.2527 $[M+Na]^+$, $C_{24}H_{50}NaOSiSn$ requires 525.2549.

Lab book reference numbers: TOR-5-437, TOR-5-439

(1*Z*,4*Z*)-1-Trimethylstannyl-6-(*tert*-butyldimethylsilyloxy)hexa-1,4-diene (183)



To a solution of alkyne **147** (461 mg, 2.19 mmol) in dry THF (20 mL) at −78 °C was added dropwise *n*-butyllithium (2.3 M in hexane, 1.0 mL, 2.30 mmol), and the resulting solution was stirred for 5 min before dropwise addition of a solution of trimethyltin chloride (480 mg, 2.41 mmol) in dry THF (5 mL). The resulting solution was stirred for 15 min at −78 °C, after which time cooling bath was removed and the reaction mixture was stirred for a further 1.5 h. The resulting solution was then diluted with ether (65 mL), washed with water (40 mL) and brine (40 mL), dried over Na_2SO_4, filtered and evaporated to afford a yellow oil which was used directly without further purification.

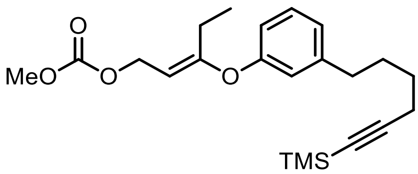
Diisobutylaluminium hydride (1.0 M in hexane, 1.05 mL, 1.05 mmol) was added dropwise to a solution of zirconocene dichloride (326 mg, 1.12 mmol) in dry THF (15 mL) at 0 °C. The reaction mixture was then stirred for 30 min at 0 °C during which time an off-white suspension formed. A solution of the crude intermediate stannane was then added in dry THF (3 mL), with additional dry THF (2 mL) used to rinse the flask and ensure quantitative transfer. The cooling was then removed, and the reaction mixture rapidly became a homogenous red solution. After stirring for 1 h, the reaction was diluted with *n*-pentane (20 mL) and quenched with water (10 eq., 125 μL), leading to the disappearance of the red colour and formation of a yellow precipitate. After stirring for 30 min, the reaction mixture was filtered through a Celite plug which was washed copiously with hexane. Evaporation of the filtrate and flash chromatography (SiO_2, petrol/ether/triethylamine, 96:2:2, *v*/*v*) afforded the *title compound* as a colourless oil (99 mg, 38%).

R_f 0.71 (ether/petrol, 1:9, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2957m, 2929m, 2857m, 1596w, 1472w, 1253m, 1098s, 836s, 774s, 719m, 527s; ^{1}H NMR (500 MHz, C_6D_6) δ 6.47 (dt, J = 12.2, 7.0 Hz, $^3J_{^{119}Sn-H}$ = 153.2 Hz, $^3J_{^{117}Sn-H}$ = 146.3 Hz, 1H), 5.94 (dt, J = 12.2, 1.1 Hz, $^2J_{^{119}Sn-H}$ = 79.0 Hz, $^2J_{^{117}Sn-H}$ = 75.9 Hz, 1H), 5.70 (dtt, J = 10.9, 6.1, 1.7 Hz, 1H), 5.43 (dtt, J = 10.9, 7.4, 1.8 Hz, 1H), 4.27 (dtt, J = 6.2, 1.6, 0.8 Hz, 2H), 2.86 (t, J = 7.1 Hz, 2H), 1.00 (s, 9H), 0.18 (s, $^2J_{^{119}Sn-H}$ = 55.0 Hz, $^2J_{^{117}Sn-H}$ = 57.7 Hz, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 146.7, 131.0, 130.2, 128.5, 59.7, 35.1, 26.1, 18.5, −4.9, −8.7 ($^1J_{^{119}Sn-C}$

= 338.9 Hz, $^{1}J_{^{117}Sn-C}$ = 322.8 Hz) ; ^{119}Sn NMR (187 MHz, C_6D_6) δ −57.7; HRMS (ESI$^+$) 399.1148 [M+Na]$^+$, $C_{15}H_{32}NaOSiSn$ requires 399.1138.

Lab book reference numbers: TOR-6-554, TOR-6-555

(*E*)-3-(3-[6-Trimethylsilyl-5-hexynyl]phenoxy)pent-2-enyl methyl carbonate (185)

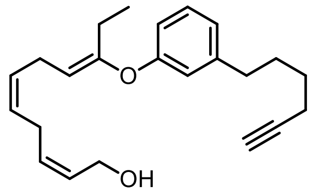


Methyl chloroformate (67 µL, 82 mg, 0.87 mmol) was added to a solution of crude alcohol **339** (0.29 mmol) and pyridine (70 µL, 69 mg, 0.45 mmol) in dry CH_2Cl_2 (5 mL) at RT. The resulting solution was stirred at RT for 2 h before being quenched with brine (5 mL), the layers separated and the aqueous layer extracted with ether (3 × 5 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (5 mL), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether/triethylamine, 80:18:2, *v*/*v*) afforded the *title compound* as a colourless oil (67.7 mg, 60% over two steps).

IR (thin film, cm^{-1}) ν_{max} 2965w, 2173w, 1746m, 1663w, 1585w, 1485w, 1443m, 1242s, 1183m, 1055w, 931m, 839s, 759m, 696m; ^{1}H NMR (400 MHz, C_6D_6) δ 7.01 (t, *J* = 7.8 Hz, 1H), 6.83 (t, *J* = 2.0 Hz, 1H), 6.80 (dt, *J* = 8.0, 1.5 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 4.82 (t, *J* = 8.1 Hz, 1H), 4.52 (d, *J* = 8.1 Hz, 2H), 3.31 (s, 3H), 2.30 (app. quin, *J* = 7.5 Hz, 4H), 2.02 (t, *J* = 7.1 Hz, 2H), 1.43–1.53 (m, 2H), 1.37–1.26 (m, 2H), 1.15 (t, *J* = 7.5 Hz, 3H), 0.22 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 165.0, 156.3, 155.4, 144.6, 129.8, 124.6, 121.3, 118.6, 107.7, 98.8, 84.8, 64.1, 54.1, 35.3, 30.5, 28.3, 23.4, 19.9, 12.6, 0.4; MS (ESI$^+$) *m/z* (rel. %) 411 ([M+Na]$^+$, 100), 335 ([M+Na−$MeOCO_2H$]$^+$, 20), 313 ([M−$MeOCO_2$]$^+$, 10); HRMS (ESI$^+$) 411.1946 [M+Na]$^+$, $C_{22}H_{32}NaO_4Si$ requires 411.1962.

Lab book reference numbers: TOR-6-476, TOR-6-477

(2*Z*, 5*Z*, 8*E*)-9-(3-hex-5-ynylphenoxy)undeca-2,5,8-trien-1-ol (186)



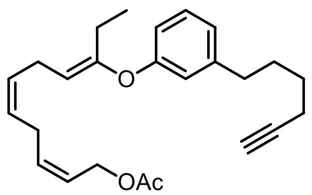
To a Schlenk tube containing a solution of *trans*-$(Ph_3P)_2Pd$(*N*-succ)Br (1.0 mg, 1.3 µmol), LiCl (5.5 mg, 0.13 mmol) and CuCl (8.4 mg, 0.09 mmol) in dry DMF (0.5 mL) was added a solution of acetate **140** (15.9 mg, 0.043 mmol) in dry DMF (0.5 mL), followed by a solution of stannane **183** (32 mg, 0.085 mmol) in dry DMF (0.5 mL). The tube was sealed and heated to 60 °C for 4.5 h, after which time the reaction mixture was cooled to RT, and diluted with ether (20 mL). The resulting solution was washed with water (3 × 10 mL), dried over $MgSO_4$, filtered and evaporated.

The crude residue was dissolved in dry THF (4 mL) and TBAF (1.0 M in THF, 0.19 mL, 0.19 mmol) was added dropwise at RT. After stirring for 2.5 h, the reaction mixture was diluted with ether (15 mL), washed with sat. aq. NH_4Cl (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, EtOAc/petrol, 1:1, *v*/*v*) afforded the *title compound* in an inseparable mixture of isomers as a yellow oil (10.6 mg, 73%, *E*/*Z* 3:1).

NMR spectroscopic data is given for the major *E*-isomer only.
R_f 0.35 (ether/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3303br, 3015w, 2936m, 1672w, 1606m, 1585m, 1485m, 1446m, 1248m, 1154s, 1045m, 782w, 696w, 634w; ^1H NMR (400 MHz, C_6D_6) δ 7.09 (t, J = 7.7 Hz, 1H), 6.98–6.90 (m, 2H), 6.72 (dt, J = 7.6, 1.3 Hz, 1H), 5.56–5.44 (m, 1H), 5.40–5.24 (m, 3H) 4.88 (t, J = 7.7 Hz, 1H), 3.94 (d, J = 6.4 Hz, 2H), 2.72–2.62 (m, 4H), 2.40–2.21 (m, 4H), 1.88 (td, J = 7.1, 2.6 Hz, 2H), 1.77 (t, J = 2.6 Hz, 1H), 1.58–1.44 (m, 2H), 1.38–1.23 (m, 2H), 1.17 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 157.1, 144.4, 130.0, 129.8, 129.7, 129.3, 123.3, 119.8, 117.0, 113.7, 107.1, 100.3, 84.2, 69.0, 58.5, 35.5, 30.5, 28.2, 26.1, 24.9, 22.7, 18.4, 12.4; MS (ESI^+) *m*/*z* (rel. %) 361 ($[M+Na]^+$, 100), 339 ($[M+H]^+$, 40); HRMS (ESI^+) 361.2126 $[M+Na]^+$, $C_{23}H_{30}NaO_2$ requires 361.2138.

Lab book reference numbers: TOR-6-518, TOR-6-519

(2*Z*, 5*Z*, 8*E*)-9-(3-hex-5-ynylphenoxy)undeca-2,5,8-trien-1-yl acetate (192)

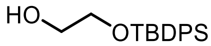


Acetic anhydride (9.3 µL, 10 mg, 0.098 mmol) was added to a solution of alcohol **186** (16.6 mg, 0.049 mmol), triethylamine (10 µL, 0.068 mmol) and DMAP (0.8 mg, 6.8 µmol) in CH_2Cl_2 (4 mL) at 0 °C. The resulting solution was stirred at RT for 1.2 h before being quenched with sat. aq. NH_4Cl (10 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and evaporated to afford the *title compound* as a colourless oil which was used without further purification (17.7 mg, 95%, *E*/*Z* 3:1).

NMR spectroscopic data is given for the major *E*-isomer only.
IR (thin film, cm^{-1}) ν_{max} 3302w, 2936m, 1739s, 1585m, 1445m, 1372m, 1228s, 1154s, 1022s, 797s, 696m; ^{1}H NMR (400 MHz, C_6D_6) δ 7.09 (t, *J* = 7.7 Hz, 1H), 6.98–6.90 (m, 2H), 6.72 (d, *J* = 7.6 Hz, 1H), 5.56–5.38 (m, 2H), 5.37–5.22 (m, 2H), 4.86 (t, *J* = 7.7 Hz, 1H), 4.58 (d, *J* = 6.6 Hz, 2H), 2.77–2.62 (m, 4H), 2.39–2.22 (m, 4H), 1.89 (td, *J* = 7.2, 2.7 Hz, 2H), 1.77 (t, *J* = 2.6 Hz, 1H), 1.66 (s, 3H), 1.57–1.43 (m, 2H), 1.39–1.24 (m, 2H), 1.17 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 194.1, 157.2, 144.4, 133.0, 129.7, 129.7, 127.2, 124.5, 123.3, 119.8, 117.0, 113.7, 107.1, 84.2, 69.0, 60.1, 35.5, 30.5, 28.2, 26.1, 24.9, 22.7, 20.5, 18.4, 12.4; MS (ESI$^+$) *m*/*z* (rel. %) 403 ([M+Na]$^+$, 100), 381 ([M+H]$^+$, 20); HRMS (ESI$^+$) 381.2400 [M+H]$^+$, $C_{25}H_{33}O_3$ requires 381.2424.

Lab book reference number: TOR-7-570

2-(*Tert*-butyldiphenylsilyloxy)ethanol (198)[285]

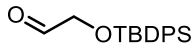


Tert-butyldiphenylsilylchloride (7.97 g, 29.0 mmol) was added dropwise over a period of 1.5 h (with the use of a syringe pump) to a solution of ethane-1,2-diol (9.0 g, 145 mmol) and triethylamine (14.7 g, 145 mmol) in CH_2Cl_2 (60 mL) at 0 °C. Upon completion of the addition, the solution was allowed to warm to RT, and stirred for a further 3 h before being quenched with water (40 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water (40 mL) and brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, EtOAc/petrol, 1:4, *v*/*v*) afforded the *title compound* as a colourless oil (1.33 g, 15%).

R_f 0.36 (ether/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3398br, 3071w, 2931m, 2858m, 1725w, 1473m, 1427m, 1391w, 1362w, 1112s, 1056m, 999m, 881w, 823m, 738m, 701s, 614m, 505s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.65 (m, 4H), 7.48–7.36 (m, 6H), 3.79–3.75 (m, 2H), 3.71–3.66 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 133.4, 130.0, 127.9, 65.0, 63.9, 27.0, 19.4; MS (ESI$^+$) *m*/*z* (rel. %) 323 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 323.1437 [M+Na]$^+$, $C_{18}H_{24}NaO_2Si$ requires 323.1438.

Lab book reference number: TOR-7-569

2-(*Tert*-butyldiphenylsilyloxy)ethanol (199)[285]

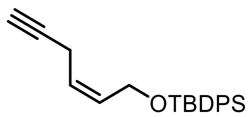


To a solution of oxalyl chloride (555 mg, 4.37 mmol) in dry CH_2Cl_2 (12 mL) was added a solution of dry DMSO (746 mg, 9.65 mmol) in dry CH_2Cl_2 (2 mL) dropwise *via* dropping funnel at −78 °C. After stirring for 10 min, a solution of alcohol **198** (1.19 g, 3.98 mmol) and dry pyridine (629 mg, 7.96 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise and the solution stirred for an additional 20 min at −78 °C. Dry triethylamine (2.01 g, 19.9 mmol) was then added dropwise and the resulting suspension allowed to warm to RT; 1M aq. HCl was added until the aqueous layer was pH 5. The layers were separated and the organic layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with sat. aq. $CuSO_4$ (10 mL) and brine (10 mL) before being dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether, 9:1, *v*/*v*) afforded the *title compound* as a colourless oil (1.06 g, 89%).

R_f 0.45 (ether/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3071w, 2932m, 2858m, 1738s, 1473m, 1427m, 1113s, 998w, 899m, 824m, 741m, 701s, 611m, 505s; ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (t, J = 0.9 Hz, 1H), 7.69–7.65 (m, 4H), 7.48–7.36 (m, 6H), 4.21 (d, J = 0.9 Hz, 2H), 1.10 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.9, 135.7, 132.6, 130.2, 128.1, 70.1, 26.8, 19.4; MS (ESI$^+$) *m*/*z* (rel. %) 321 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 321.1280 [M+Na]$^+$, $C_{18}H_{22}NaO_2Si$ requires 321.1281.

Lab book reference number: TOR-7-572

(*Z*)-6-(*Tert*-butyldiphenylsilyloxy)hex-4-en-1-yne (200)

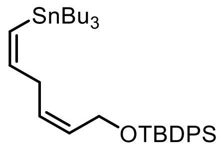


To a rapidly stirred suspension of phosphonium salt **162** (1.71 g, 4.64 mmol) in dry THF (12 mL) at −78 °C was added dropwise *n*-butyllithium (2.3 M in hexanes, 1.81 mL, 4.16 mmol). After stirring for 5 min at −78 °C, the resulting solution was warmed to 0 °C for 40 min, before being cooled to −78 °C, and a solution of aldehyde **199** (1.08 g, 3.62 mmol) in dry THF (4 mL) was added dropwise *via* syringe. Transfer was made quantitative with an additional portion of dry THF (4 mL). The resulting reaction mixture was stirred at −78 °C for 1.5 h before being allowed to warm to RT. After a further 6 h at RT, the reaction was quenched with sat. aq. NH_4Cl (25 mL), and the aqueous later extracted with ether (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether, 9:1, *v*/*v*) afforded the *title compound* as a pale yellow oil (946 mg, 78%).

R_f 0.68 (ether/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3304m, 3072w, 2931m, 2858m, 1473m, 1428m, 1362w, 1113s, 1071m, 998w, 824m, 741m, 702s, 639m, 614m, 505s; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (m, 4H), 7.46–7.36 (m, 6H), 5.75–5.64 (m, 1H), 5.47 (dtt, J = 10.6, 7.0, 1.7 Hz, 1H), 4.25 (ddt, J = 6.1, 1.7, 0.8 Hz, 2H), 2.79 (dddt, J = 7.0, 2.6, 1.7, 0.9 Hz, 2H), 1.94 (t, J = 2.7 Hz, 1H), 1.04 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 133.7, 131.2, 129.8, 127.9, 124.9, 82.4, 68.4, 60.2, 26.9, 19.3, 17.4; MS (ESI$^+$) *m*/*z* (rel. %) 357 ($[M+Na]^+$, 100), 335 ($[M+H]^+$, 20); HRMS (ESI$^+$) 357.1637 $[M+Na]^+$, $C_{22}H_{26}NaOSi$ requires 357.1645.

Lab book reference number: TOR-7-574

(1*Z*,4*Z*)-1-Tri-*n*-butylstannyl-6-(*tert*-butyldiphenylsilyloxy)hexa-1,4-diene (202)



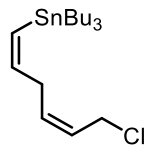
To a solution of alkyne **200** (947 mg, 2.83 mmol) in dry THF (20 mL) at −78 °C was added dropwise *n*-butyllithium (2.3 M in hexanes, 1.25 mL, 2.89 mmol), and the resulting solution was stirred for 5 min before dropwise addition of tributyltin chloride (1.01 g, 3.11 mmol). The resulting solution was stirred for 30 min at −78 °C, after which time cooling bath was removed and the reaction mixture was stirred for a further 2 h. The resulting solution was then diluted with petrol (100 mL), washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and evaporated to afford a yellow oil which was used directly without further purification.

Diisobutylaluminium hydride (1.0 M in hexane, 4.3 mL, 4.30 mmol) was added dropwise to a solution of zirconocene dichloride (1.32 g, 4.53 mmol) in dry THF (15 mL) at 0 °C. The reaction mixture was then stirred for 45 min at 0 °C during which time an off-white suspension formed. A solution of the crude intermediate stannane (2.83 mmol) was then added in dry THF (3 mL), with additional dry THF (2 mL) used to rinse the flask and ensure quantitative transfer. The cooling was then removed, and the reaction mixture rapidly became a homogenous red solution. After stirring for 1 h, the reaction was diluted with *n*-pentane (20 mL) followed by water (10 eq., 0.5 mL). After stirring for 2.5 h, a further portion of water (0.5 mL) was added, leading to the disappearance of the red colour and formation of a yellow solution containing a white precipitate. The reaction mixture was filtered through a Celite plug which was washed copiously with hexane. Evaporation of the filtrate and flash chromatography (SiO_2, petrol/ether/triethylamine, 95:3:2, *v*/*v*) afforded the *title compound* as a colourless oil (1.51 g, 85%).

R_f 0.78 (ether/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2957s, 2928s, 2856m, 1591w, 1463m, 1428m, 1376w, 1111s, 1071m, 999w, 824m, 740m, 701s, 613m, 505s; ^{1}H NMR (400 MHz, C_6D_6) δ 7.85–7.77 (m, 4H), 7.27–7.21 (m, 6H), 6.46 (dt, J = 12.3, 7.1 Hz, 1H), 5.97 (dt, J = 12.3, 1.2 Hz, 1H), 5.82 (dtt, J = 10.8, 6.2, 1.6 Hz, 1H), 5.56–5.42 (m, 1H), 4.41 (ddt, J = 6.2, 1.6, 0.8 Hz, 2H), 2.82–2.70 (m, 2H), 1.62–1.51 (m, 6H), 1.41–1.29 (m, 6H), 1.19 (s, 9H), 0.99–0.94 (m, 6H), 0.92 (t, J = 7.3 Hz, 9H); ^{13}C NMR (101 MHz, C_6D_6) δ 147.0, 136.0, 134.2, 130.3, 130.0, 129.1, 100.3, 77.0, 60.7, 35.9, 29.7, 27.7, 27.1, 19.5, 14.0, 10.6; MS (ESI$^+$) *m*/*z* (rel. %) 358 ($[M-SnBu_3+H+Na]^+$, 100), 649 ($[M+Na]^+$, 20), 665 ($[M+K]^+$, 15); HRMS (ESI$^+$) 649.2856 $[M+Na]^+$, $C_{34}H_{53}NaOSiSn$ requires 649.2858.

Lab book reference numbers: TOR-7-576, TOR-7-578

(1*Z*,4*Z*)-1-Tri-*n*-butylstannyl-6-chlorohexa-1,4-diene (204)



To a solution of silyl ether **202** (356 mg, 0.57 mmol) in dry THF (10 mL) was added dropwise TBAF (1 M in THF, 0.6 mL, 0.60 mmol) at RT. After 1.5 h, the reaction mixture was diluted with ether (40 mL), washed with sat. aq. NH_4Cl (20 mL), dried over Na_2SO_4, filtered and evaporated to afford a crude allylic alcohol which was used directly without further purification.

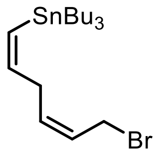
To a solution of the crude allylic alcohol in dry CH_2Cl_2 (5 mL) was added triphenylphosphine (224 mg, 0.86 mmol) and carbon tetrachloride (110 μL, 1.14 mmol). After stirring for 5 h, an additional portion of carbon tetrachloride (55 μL, 0.57 mmol) was added. After stirring for 22 h, a further portion of carbon tetrachloride (275 μL, 2.85 mmol) was added, and this process was repeated after a further 2 h. After a total reaction time of 29 h, the solvent was removed *in vacuo*. Flash chromatography (SiO_2, *n*-pentane/ether/triethylamine, 95:2:3, *v*/*v*) afforded the *title compound* as a colourless oil (55.2 mg, 24%).

IR (thin film, cm^{-1}) ν_{max} 2957s, 2924s, 2872m, 2853m, 1595w, 1464m, 1377w, 1251w, 1072w, 874w, 767w, 693w, 597w; ^{1}H NMR (400 MHz, C_6D_6) δ 6.43 (dt, J = 12.3, 7.0 Hz, 1H), 6.01 (dt, J = 12.3, 1.2 Hz, 1H), 5.55–5.41 (m, 2H), 3.76 (d, J = 7.0 Hz, 2H), 2.79 (ddd,

J = 6.8, 5.5, 1.3 Hz, 2H), 1.65–1.52 (m, 6H), 1.43–1.31 (m, 6H), 1.03–0.97 (m, 6H), 0.94 (t, J = 7.3 Hz, 9H); ^{13}C NMR (101 MHz, C_6D_6) δ 146.0, 132.8, 130.0, 126.4, 39.1, 35.1, 29.7, 27.7, 14.0, 10.6.

Lab book reference numbers: TOR-7-585, TOR-7-586

(1*Z*,4*Z*)-1-Tri-*n*-butylstannyl-6-bromohexa-1,4-diene (205)



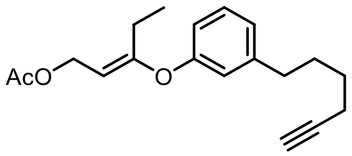
To a solution of silyl ether **202** (412 mg, 0.66 mmol) in dry THF (10 mL) was added dropwise TBAF (1 M in THF, 0.69 mL, 0.69 mmol) at RT. After 1.5 h, the reaction mixture was diluted with ether (40 mL), washed with sat. aq. NH_4Cl (20 mL), dried over Na_2SO_4, filtered and evaporated to afford a crude allylic alcohol which was used directly without further purification.

To a solution of the crude allylic alcohol in dry CH_2Cl_2 (5 mL) was added triphenylphosphine (207 mg, 0.79 mmol) and carbon tetrabromide (251 mg, 0.76 mmol). After stirring for 6 h, additional portions of carbon tetrabromide (109 mg, 0.33 mmol) and triphenylphosphine (86 mg, 0.33 mmol) were added. After stirring for a further 1 h, the solvent was removed *in vacuo*, hexane (20 mL) was added, and the resulting precipitate removed by filtration. Evaporation of the filtrate and flash chromatography (SiO_2, petrol/ether/triethylamine, 95:2:3, *v*/*v*) afforded the *title compound* as a colourless oil (131 mg, 44%).

IR (thin film, cm^{-1}) ν_{max} 2956s, 2924s, 2871m, 2853m, 1594w, 1464m, 1377w, 1204m, 1072w, 874w, 755w, 693m, 598w; ^{1}H NMR (400 MHz, C_6D_6) δ 6.45 (dt, J = 12.3, 7.0 Hz, 1H), 6.02 (dt, J = 12.3, 1.3 Hz, 1H), 5.58–5.49 (m, 1H), 5.41 (dt. J = 10.5, 7.3 Hz, 1H), 3.63 (d, J = 8.2 Hz, 2H), 2.82 (tt, J = 7.2, 1.5 Hz, 2H), 1.69–1.51 (m, 6H), 1.47–1.29 (m, 6H), 1.07–0.89 (m, 15H); ^{13}C NMR (101 MHz, C_6D_6) δ 145.8, 133.2, 130.0, 126.4, 34.9, 29.7, 27.7, 26.6, 14.0, 10.6.

Lab book reference numbers: TOR-7-580, TOR-7-581

(*E*)-3-(3-[5-Hexynyl]phenoxy)pent-2-enyl acetate (196)

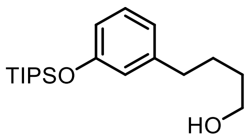


To a solution of silyl protected alkyne **140** (48.4 mg, 0.130 mmol) in dry THF (5 mL) was added TBAF (1 M in THF, 0.14 mL, 0.14 mmol), and the resulting solution stirred at RT for 2 h. The reaction mixture was then diluted with ether (30 mL), washed with sat. aq. NH_4Cl (15 mL), dried over $MgSO_4$, filtered and evaporated. Flash chromatography (SiO_2, petrol/ether, 17:3, *v*/*v*) afforded the *title compound* as a colourless oil (20.5 mg, 53%).

R_f 0.56 (ether/petrol, 2:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3296w, 2940m, 1737s, 1665m, 1606w, 1586m, 1485m, 1444w, 1365m, 1230s, 1181s, 1151m, 1055w, 1020m, 971w, 946w, 801w, 697w, 637w; ^{1}H NMR (400 MHz, C_6D_6) δ 7.03 (t, *J* = 7.7 Hz, 1H), 6.88–6.82 (m, 2H), 6.73 (dt, *J* = 7.4, 1.3 Hz, 1H), 4.84 (t, *J* = 8.0 Hz, 1H), 4.52 (d, *J* = 8.0 Hz, 2H), 2.31 (q, *J* = 7.5 Hz, 2H), 2.27 (t, *J* = 7.8 Hz, 2H), 1.88 (td, *J* = 7.1, 2.7 Hz, 2H), 1.76 (t, *J* = 2.7 Hz, 1H), 1.63 (s, 3H), 1.50–1.41 (m, 2H), 1.30–1.23 (m, 2H), 1.15 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 164.0, 155.6, 144.6, 129.8, 128.7, 124.5, 121.2, 118.6, 99.7, 84.1, 69.0, 60.6, 35.3, 30.4, 28.2, 23.4, 20.6, 18.4, 12.6; MS (ESI$^+$) *m*/*z* (rel. %) 241 ($[M-AcO]^+$, 45), 263 ($[M-OAc+Na]^+$, 100), 279 ($[M-OAc+K]^+$, 2), 323 ($[M+Na]^+$, 80), 339 ($[M+K]^+$, 10); HRMS (ESI$^+$) 323.1606 $[M+Na]^+$, $C_{19}H_{24}NaO_3$ requires 323.1618.

Lab book reference number: TOR-7-582

4-[3-(Triisopropylsilanyloxy)-phenyl]-butan-1-ol (215)



A solution of 3-iodophenol (5.0 g, 22.75 mmol), triisopropylchlorosilane (5.8 mL, 27.3 mmol) and imidazole (1.86 g, 27.3 mmol) in CH_2Cl_2 (50 mL) was stirred for 2 h at RT. After this time, the reaction mixture was poured onto ice water (50 mL), the layers separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with 1 M aq. HCl (50 mL), 1 M aq. NaOH (50 mL) and sat. aq. $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered and evaporated to afford a colourless oil which was used directly without purification.

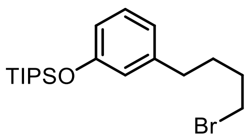
A stirred solution of the crude protected phenol (22.75 mmol), $PdCl_2(PPh_3)_2$ (160 mg, 0.23 mmol), CuI (43 mg, 0.23 mmol) and 3-butyn-1-ol (1.91 g, 27.3 mmol) in dry triethylamine (60 mL) was heated to 70 °C for 1 h. After this time, the resulting mixture was cooled to RT, and quenched with sat. aq. NH_4Cl (300 mL). The aqueous solution was extracted with CH_2Cl_2 (3 × 250 mL), and the combined organic layers washed with brine (250 mL), dried over $MgSO_4$, filtered and evaporated to afford a yellow oil which was used directly without further purification.

Palladium on carbon (1 g, 10 wt%, 5 wt% Pd) was added to a stirred solution of the crude alkyne (22.75 mmol) in MeOH (100 mL). The reaction vessel was then placed under an atmosphere of H_2 and stirred for 48 h, after which time the reaction mixture was filtered through a short plug of silica which was washed thoroughly with CH_2Cl_2. Evaporation afforded the *title compound* as a colourless oil (7.13 g, 97% over three steps).

R_f 0.33 (ether/petrol, 1:1); IR (thin film, cm^{-1}) ν_{max} 3345br, 2942s, 2866s, 1602m, 1584s, 1484s, 1463m, 1441m, 1384w, 1276s, 1158m, 1061m, 1003m, 976m, 920w, 883s, 826m, 782m, 687s, 509w, 455w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.07 (m, 1H), 6.77–6.73 (m, 1H), 6.74–6.64 (m, 2H), 3.66 (t, J = 6.4 Hz, 2H), 2.58 (t, J = 7.4 Hz, 2H), 1.71–1.63 (m, 2H), 1.63–1.55 (m, 2H), 1.34–1.16 (m, 3H), 1.09 (d, J = 7.2 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 143.9, 129.2, 121.3, 120.2, 117.4, 63.0, 35.7, 32.4, 27.6, 18.1, 12.8; MS (ESI$^+$) m/z (rel. %) 323 ([M+H]$^+$, 40), 345 ([M+Na]$^+$, 100), 361 ([M+K]$^+$, 10); HRMS (ESI$^+$) 323.2401 [M+H]$^+$, $C_{19}H_{35}NaO_2Si$ requires 323.2401.

Lab book reference number: TOR-7-660, TOR-7-661, TOR-7-662

1-Bromo-4-[3-(triisopropylsilanyloxy)-phenyl]-butane (216)

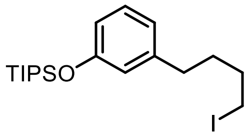


A solution of alcohol **215** (591 mg, 1.83 mmol), carbon tetrabromide (911 mg, 2.75 mmol) and triphenylphosphine (721 mg, 2.75 mmol) in dry ether (10 mL) was stirred at RT for 16 h. After this time TLC analysis indicated incomplete reaction, so additional portions of carbon tetrabromide (304 mg, 0.92 mmol) and triphenylphosphine (240 mg, 0.92 mmol) were added. After an additional 2 h, the reaction mixture was filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/EtOAc, 9:1, *v*/*v*) afforded the title compound as a colourless oil (652 mg, 92%).

R_f 0.59 (ether/petrol, 1:9, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2943m, 2893w, 2866m, 1602m, 1584m, 1484s, 1463m, 1441m, 1278s, 1158m, 1003m, 970m, 882s, 823m, 681s, 659m, 563w, 510w, 458w; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (td, J = 7.4, 1.6 Hz, 1H), 6.76–6.73 (m, 1H), 6.75–6.66 (m, 2H), 3.41 (t, J = 6.7 Hz, 2H), 2.58 (t, J = 7.5 Hz, 2H), 1.93–1.81 (m, 2H), 1.81–1.68 (m, 2H), 1.29–1.18 (m, 3H), 1.10 (d, J = 7.2 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 143.3, 129.2, 121.2, 120.1, 117.5, 34.9, 33.7, 32.2, 29.7, 18.0, 12.8; MS (ESI^+) *m*/*z* (rel. %) 385 ($[M+H]^+$, 100), 407 ($[M+Na]^+$, 95); HRMS (ESI^+) 385.1559 $[M+H]^+$, $C_{19}H_{34}BrOSi$ requires 385.1557.

Lab book reference number: TOR-7-645

1-Iodo-4-[3-(triisopropylsilanyloxy)-phenyl]-butane (217)



METHOD A: A stirred solution of bromide **216** (210 mg, 0.55 mmol) and NaI (164 mg, 1.09 mmol) in acetone (10 mL) was heated to 60 °C for 2 h. After this time the reaction mixture was cooled to RT, diluted with water (40 mL) and extracted with ether (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford the *title compound* as a colourless oil (231 mg, 98%).

METHOD B: Iodine (868 mg, 3.42 mmol) was added portion-wise to a solution of triphenylphosphine (897 mg, 3.42 mmol) and imidazole (464 mg, 6.82 mmol) in CH_2Cl_2 (15 mL), and the resulting mixture stirred for 30 min at RT. A solution of alcohol **215** (1.0 g, 3.10 mmol) in CH_2Cl_2 (5 mL) was then added dropwise and the reaction stirred for a further 15 min. After this time the reaction was quenched with sat. aq. $Na_2S_2O_4$ (20 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/ether, 19:1, *v*/*v*) afforded the *title compound* as a colourless oil (1.03 g, 73%).

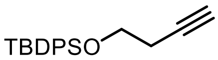
R_f 0.62 (ether/petrol, 1:9, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2943s, 2866s, 1603m, 1584m, 1484s, 1463m, 1442m, 1279s, 1158m, 1072w, 1003m, 973m, 883s, 822m, 780m, 689s, 510w; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (td, J = 7.5, 1.0 Hz, 1H), 6.74 (dt, J = 7.7, 1.3 Hz, 1H), 6.72–6.68 (m, 2H), 3.19 (t, J = 6.9 Hz, 2H), 2.57 (t, J = 7.5 Hz, 2H), 1.89–1.77 (m, 2H), 1.77–1.65 (m, 2H), 1.30–1.18 (m, 3H), 1.10 (d, J = 7.2 Hz, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 143.4, 129.3, 121.3, 120.2, 117.5, 34.8, 33.0, 32.2, 18.0, 12.8, 6.9;

MS (ESI$^+$) m/z (rel. %) 455 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 455.1240 [M+Na]$^+$, $C_{19}H_{33}INaOSi$ requires 455.1238.

Lab book reference number (method A): TOR-7-653

Lab book reference number (method B): TOR-8-678

(But-3-ynyloxy)*tert*-butyldiphenylsilane (211)

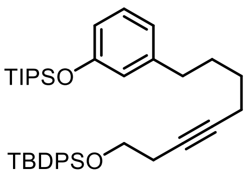


To a stirred solution of 3-butyn-1-ol (2.5 g, 35.7 mmol) and imidazole (2.55 g, 35.7 mmol) in CH_2Cl_2 (200 mL) was added dropwise *tert*-butyldiphenylchlorosilane (9.27 mL, 35.7 mmol). The resulting mixture was stirred for 26 h at RT, before being filtered through a short plug of silica gel, eluting with CH_2Cl_2. The solution was concentrated *in vacuo* to afford the *title compound* as a colourless oil (10.85 g, 99%).

R_f 0.54 (ether/petrol, 1:9, v/v); IR (thin film, cm^{-1}) ν_{max} 3309w, 3072w, 2931m, 2858m, 1473m, 1428m, 1384w, 1106s, 1008w, 918m, 823m, 799w, 737m, 700s, 613s, 503s, 488s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (m, 4H), 7.45–7.35 (m, 6H), 3.79 (t, J = 7.1 Hz, 2H), 2.45 (td, J = 7.1, 2.7 Hz, 2H), 1.95 (t, J = 2.7 Hz, 1H), 1.06 (s, 9H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 133.7, 129.8, 127.8, 81.6, 69.5, 62.4, 26.9, 22.7, 19.4; MS (APCI$^+$) m/z (rel. %) 309 ([M+H]$^+$, 100); HRMS (APCI$^+$) 309.1661 [M+H]$^+$, $C_{20}H_{25}OSi$ requires 309.1669.

Lab book reference number: TOR-8-711

1-*tert*-Butyldiphenylsilyloxy-8-[3-(triisopropylsilanyloxy)-phenyl]-oct-3-yne (218)

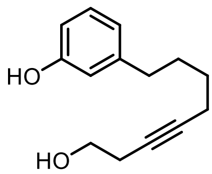


To a stirred solution of alkyne **211** (122 mg, 0.396 mmol) in dry THF (5 mL) at −78 °C was added dropwise n-butyllithium (1.85 M in hexanes, 0.22 mL, 0.396 mmol). The resulting solution stirred for 25 min, before the addition of a solution of iodide **217** (150 mg, 0.33 mmol) and HMPA (140 µL, 0.792 mmol) in dry THF (1 mL). An additional portion of dry THF (1 mL) was used to ensure quantitative transfer. The reaction mixture was then stirred for 5 min at −78 °C, 1 h at RT, and 5 h at 66 °C. After this time the reaction was cooled to RT and quenched with sat. aq. NH_4Cl (10 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic layers were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/$CHCl_3$, 4:1→1:1, *v*/*v*) afforded the *title compound* as a colourless oil (40.8 mg, 20%).

R_f 0.58 (ether/petrol, 1:9, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2941s, 2865m, 1584m, 1484m, 1277s, 1157m, 1110s, 1003w, 883m, 823m, 738w, 701s, 614w, 506s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4H), 7.45–7.34 (m, 6H), 7.09 (dd, J = 8.8, 7.5 Hz, 1H), 6.72 (dt, J = 7.5, 1.3 Hz, 1H), 6.70–6.67 (m, 2H), 3.73 (t, J = 7.2 Hz, 2H), 2.53 (t, J = 7.6 Hz, 2H), 2.42 (tt, J = 7.2, 2.4 Hz, 2H), 2.13 (tt, J = 7.1, 2.4 Hz, 2H), 1.66 (tt, J = 9.0, 6.7 Hz, 2H), 1.53–1.42 (m, 2H), 1.33–1.17 (m, 3H), 1.09 (d, J = 7.2 Hz, 18H), 1.05 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 144.0, 135.7, 133.9, 129.7, 129.2, 127.8, 121.3, 120.2, 117.3, 81.3, 76.8, 63.1, 35.4, 30.6, 28.6, 26.9, 23.1, 19.4, 18.8, 18.1, 12.8; MS (ESI$^+$) *m*/*z* (rel. %) 635 ([M+Na]$^+$, 100), 651 ([M+K]$^+$, 80); HRMS (ESI$^+$) 635.3725 [M+Na]$^+$, $C_{39}H_{56}NaO_2Si_2$ requires 635.3711.

Lab book reference number: TOR-8-687

3-[8-Hydroxyoct-5-ynyl]-phenol (219)

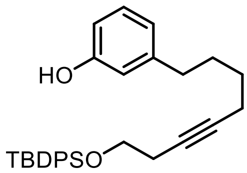


To a solution of bis-silyl-protected compound **218** (19.4 mg, 0.032 mmol) in dry THF (1 mL) was added TBAF (1 M in THF, 33 µL, 0.033 mmol) at 0 °C. After 45 min, the reaction was quenched with sat. aq. NH_4Cl (10 mL). The aqueous layer was then extracted with ether (3 × 10 mL), and the organic layers combined, dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/EtOAc, 9:1→4:1, *v*/*v*) afforded the *title compound* as a colourless oil (6.7 mg, 96%).

R_f 0.09 (EtOAc/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3312br, 2931m, 2856m, 1588s, 1457s, 1260s, 1156s, 1041s, 782m, 695m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, J = 7.8 Hz, 1H), 6,74 (ddd, J = 7.5, 1.6, 0.9 Hz, 1H), 6.70 (t, J = 1.9 Hz, 1H), 6.68–6.64 (m, 1H), 5.28 (br s, 1H), 3.70 (t, J = 6.1 Hz, 2H), 2.59 (t, J = 7.5 Hz, 2H), 2.44 (tt, J = 6.1, 2.4 Hz, 2H), 2.19 (tt, J = 7.0, 2.4 Hz, 2H), 1.91 (br s, 1H), 1.77–1.68 (m, 2H), 1.56–1.47 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 144.3, 129.6, 121.1, 115.3, 112.9, 82.7, 76.7, 61.5, 35.1, 30.1, 28.3, 23.3, 18.7; MS (ESI$^+$) *m*/*z* (rel. %) 219 ([M+H]$^+$, 100), 241 ([M+Na]$^+$, 80); HRMS (ESI$^+$) 219.1378 [M+Na]$^+$, $C_{14}H_{19}O_2$ requires 219.1380.

Lab book reference number: TOR-8-669

3-([8-*tert*-Butyldiphenylsilyl]oct-5-ynyl)phenol (220)



METHOD A, INITIAL REACTION: To a suspension of potassium *tert*-butoxide (267 mg, 2.38 mmol) and dry TMEDA (214 µL, 2.38 mmol) in dry hexane (5 mL) at −78 °C was added dropwise *n*-butyllithium (1.8 M in hexanes, 1.32 mL, 2.38 mmol), and the mixture was stirred for 15 min. After this time, *m*-cresol (100 µL, 0.95 mmol) was added, and the reaction mixture was warmed to −20 °C and stirred at this temperature for 3 h. The cooling bath was then removed, dry THF (2 mL) added, and the reaction cooled to −78 °C before a solution of iodide **222** (702 mg, 1.47 mmol) in dry THF (3 mL) was added. The resulting mixture was stirred at −78 °C for 2 h before being quenched with water (8 mL) and 6 M aq. HCl (1 mL). The layers were separated, and the aqueous layer extracted with ether (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/EtOAc, 92:8, *v*/*v*) and drying *in vacuo* afforded the *title compound* as a colourless oil (211 mg, 44%).

METHOD A, OPTIMISED PROCEDURE: To a suspension of potassium *tert*-butoxide (1.10 g, 9.8 mmol) and dry TMEDA (1.47 mL, 9.8 mmol) in dry hexane (21 mL) at −78 °C was added dropwise *n*-butyllithium (2.0 M in hexanes, 4.87 mL, 9.8 mmol), and the mixture was stirred for 15 min. After this time, *m*-cresol (410 µL, 3.9 mmol) was added, and the reaction mixture was warmed to −20 °C and stirred at this temperature for 3.5 h. The cooling bath was then removed, dry THF (5 mL) added, and the reaction cooled to −78 °C before a solution of iodide **222** (2.8 g, 5.9 mmol) in dry THF (8 mL) was added. The resulting mixture was stirred at −78 °C for 20 h before being quenched with brine (20 mL) and 6 M aq. HCl (5 mL). The layers were separated, and the aqueous layer extracted with ether (4 × 30 mL). The combined organic layers were washed with water (5 mL), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/EtOAc, 19:1→17:3, *v*/*v*) and drying *in vacuo* afforded the *title compound* as a colourless oil (1.27 g, 71%).

METHOD B: A solution of bis-silyl ether **218** (63.4 mg, 0.10 mmol) and potassium acetate (5 mg, 0.05 mmol) in DMF/water (20:1, 0.7 mL) was stirred at 70 °C for 22 h. After this time the reaction mixture was cooled to RT, diluted with ether (10 mL) and washed with water (3 × 5 mL). The aqueous layer was extracted with ether (5 mL), and the combined organic layers washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/EtOAc, 9:1, *v*/*v*) afforded the *title compound* as a colourless oil (43.4 mg, 95%).

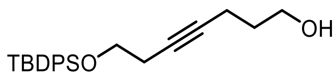
R_f 0.46 (ether/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3397br, 2928s, 2856m, 1589m, 1456m, 1428m, 1155w, 1111s, 823w, 738m, 701s, 613m, 505s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.66 (m, 4H), 7.45–7.33 (m, 6H), 7.12 (td, *J* = 7.4, 1.2 Hz, 1H), 6.73 (dt, *J* = 7.7, 1.2 Hz, 1H), 6.67–6.60 (m, 2H), 4.57 (br s, 1H), 3.74 (t, *J* = 7.1 Hz, 2H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.42 (tt, *J* = 7.1, 2.4 Hz, 2H), 2.14 (tt, *J* = 7.0, 2.4 Hz, 2H), 1.68 (tt, *J* = 9.0, 6.7 Hz, 2H), 1.49 (quin, *J* = 7.2 Hz, 2H), 1.04 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 144.5, 135.7, 133.9, 129.8, 129.6, 127.8, 121.1, 115.4, 112.7, 81.3, 77.31, 63.1, 35.4, 30.4, 28.6, 26.9, 23.1, 19.4, 18.8; MS (ESI$^+$) *m*/*z* (rel. %) 457 ($[M+H]^+$, 5), 474 ($[M+NH_4]^+$, 100), 479 ($[M+Na]^+$, 80), 495 ($[M+K]^+$, 40); HRMS (ESI$^+$) 479.2381 $[M+Na]^+$, $C_{30}H_{36}NaO_2Si$ requires 479.2377.

Lab book reference number (method A, initial reaction): TOR-8-710

Lab book reference number (method A, optimised procedure): MV-1-018 (*reaction optimised by M. Völkel*)

Lab book reference number (method B): TOR-8-707

7-(*tert*-Butyldiphenylsilyloxy)hept-4-yn-1-ol (221)

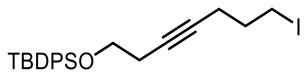


To a solution of alkyne **211** (5 g, 16.2 mmol) in dry THF (30 mL) was added dropwise *n*-butyllithium (2.0 M in hexanes, 8.1 mL, 16.2 mmol) at −78 °C. The reaction mixture was stirred for 25 min before the addition of BF_3•Et_2O (2.0 mL, 16.2 mmol), and the resulting solution stirred for a further 15 min. After this time trimethylene oxide (526 µL, 8.1 mmol) was added dropwise and the reaction mixture maintained at −78 °C for a further 2 h. After this time, the cooling was removed and the reaction immediately quenched with sat. aq. NH_4Cl (60 mL). The layers were separated and the aqueous layer extracted with ether (3 × 60 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether, 9:1→1:1, *v*/*v*) afforded the *title compound* as a colourless oil (2.71 g, 91%).

R_f 0.25 (ether/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2245br, 3071w, 2931m, 2858m, 1473m, 1428m, 1389w, 1361w, 1101s, 1057m, 916w, 823m, 738m, 701s, 688m, 614m, 505s, 490m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (m, 4H), 7.46–7.35 (m, 6H), 3.75 (t, J = 7.1 Hz, 2H), 3.72 (t, J = 6.2 Hz, 2H), 2.42 (tt, J = 7.1, 2.4 Hz, 2H), 2.26 (tt, J = 6.9, 2.4 Hz, 2H), 1.71 (tt, J = 6.9, 6.2 Hz, 2H), 1.05 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 133.8, 129.8, 127.8, 80.7, 77.9, 63.0, 62.1, 31.6, 26.9, 23.0, 19.4, 15.5; MS (ESI$^+$) *m*/*z* (rel. %) 389 ([M+H]$^+$, 100); HRMS (ESI$^+$) 389.1906 [M+H]$^+$, $C_{23}H_{30}NaO_2Si$ requires 389.1907.

Lab book reference number: TOR-8-684

7-(*tert*-Butyldiphenylsilyloxy)-1-iodohept-4-yne (222)



INITIAL REACTION: A solution of alcohol **221** (983 mg, 2.68 mmol), triphenylphosphine (1.06 g, 4.02 mmol), iodine (1.02 g, 4.02 mmol) and imidazole (274 mg, 4.02 mmol) in MeCN (30 mL) was stirred at RT for 4 h. After this time, the solvent was removed *in vacuo*, and the residue dissolved in ether (60 mL) and washed with sat. aq. $Na_2S_2O_4$ (40 mL). The layers were separated and the aqueous layer extracted with ether (2 × 40 mL). The combined organic layers were then washed with brine (40 mL), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether, 99:1, *v*/*v*) afforded the *title compound* as a colourless oil (929 mg, 73%).

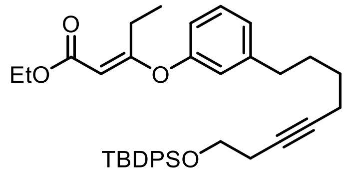
OPTIMISED PROCEDURE: A solution of alcohol **221** (4.85 g, 13.2 mmol), triphenylphosphine (3.85 g, 14.6 mmol), iodine (3.71 g, 14.6 mmol) and imidazole (1.98 g, 29.1 mmol) in CH_2Cl_2 (100 mL) was stirred at RT for 3 h. After this time, the reaction mixture was quenched with 10% aq. $Na_2S_2O_4$ (50 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were then dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether, 19:1, *v*/*v*) afforded the *title compound* as a colourless oil (5.53 mg, 88%).

R_f 0.50 (ether/petrol, 1:9, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3070w, 2931m, 2857m, 1472w, 1428m, 1221w, 1111s, 823m, 738m, 701s, 614m, 505s, 490m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (m, 4H), 7.46–7.36 (m, 6H), 3.74 (t, J = 7.0 Hz, 2H), 3.27 (t, J = 6.8 Hz, 2H), 2.41 (tt, J = 7.0, 2.4 Hz, 2H), 2.27 (tt, J = 6.7, 2.4 Hz, 2H), 1.94 (quin, J = 6.7 Hz, 2H), 1.05 (s, 9H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 133.8, 129.8, 127.8, 79.2, 78.5, 62.9, 41.7, 32.6, 26.9, 23.1, 19.9, 19.4; MS (ESI$^+$) *m*/*z* (rel. %) 477 ([M+H]$^+$, 10), 494 ([M+NH_4]$^+$, 100); HRMS (ESI$^+$) 477.1100 [M+H]$^+$, $C_{23}H_{30}IO_4Si$ requires 477.1105.

Lab book reference number (initial reaction): TOR-7-627

Lab book reference number (optimised procedure): MV-1-058 (*reaction optimised by M. Völkel*)

Ethyl (*E*)-3-(3-[8-*tert*-butyldiphenylsilyloxyoct-5-ynyl]phenoxy)pent-2-enoate (223)

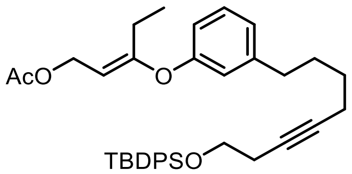


A flame-dried Schlenk tube containing a stirrer bar was charged with K_3PO_4 (323 mg, 1.52 mmol), followed by a solution of triflate ***E*-134** (212 mg, 0.76 mmol) in dry toluene (2 mL), a premixed solution of $Pd(OAc)_2$ (4.3 mg, 0.02 mmol) and X-Phos (18 mg, 0.04 mmol) in dry toluene (2 mL) and a solution of phenol **220** (417 mg, 0.91 mmol) in dry toluene (2 mL). The resulting suspension was heated to 100 °C for 2 h. The reaction mixture was then cooled to RT, filtered through a pad of Celite and evaporated. Purfication by flash chromatography (SiO_2, petrol/ether, 19:1, *v*/*v*) afforded the *title compound* as a colourless oil (226 mg, 51%).

R_f 0.59 (ether/petrol, 2:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2932m, 2858m, 1712s, 1632s, 1608w, 1584w, 1485w, 1463w, 1428m, 1377m, 1242m, 1223m, 1182w, 1128s, 1112s, 1046s, 999w, 917w, 823m, 738m, 701s, 613m, 505s, 490m; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.67 (m, 4H), 7.46–7.36 (m, 6H), 7.32–7.21 (m, 1H), 7.02 (dt, *J* = 7.7, 1.5 Hz, 1H), 6.88–6.78 (m, 2H), 4.79 (s, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.76 (t, *J* = 7.1 Hz, 2H), 2.95 (q, *J* = 7.5 Hz, 2H), 2.64–2.58 (m, 2H), 2.44 (tt, *J* = 7.1, 2.4 Hz, 2H), 2.17 (tt, *J* = 7.0, 2.4 Hz, 2H), 1.76–1.66 (m, 2H), 1.56–1.46 (m, 2H), 1.29 (t, *J* = 7.5 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 167.6, 153.6, 144.9, 135.7, 133.9, 129.8, 129.7, 127.8, 125.8, 121.5, 118.9, 95.1, 81.1, 77.4, 63.0, 59.6, 35.3, 30.4, 28.6, 26.9, 25.1, 23.1, 19.3, 18.7, 14.4, 12.0; MS (ESI^+) *m*/*z* (rel. %) 583 ($[M+H]^+$, 5), 600 ($[M+NH_4]^+$, 80), 605 ($[M+Na]^+$, 100), 621 ($[M+K]^+$, 5); HRMS (ESI^+) 605.3063 $[M+Na]^+$, $C_{37}H_{46}NaO_4Si$ requires 605.3058.

Lab book reference number: TOR-8-718

(*E*)-3-(3-[8-*tert*-Butyldiphenylsilyloxyoct-5-ynyl]phenoxy)pent-2-enyl acetate (224)



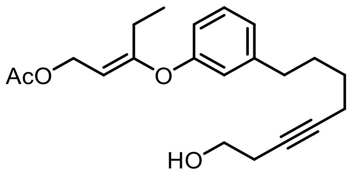
Diisobutylaluminium hydride (1.0 M in hexanes, 0.79 mL, 0.79 mmol) was added to a solution of ester **223** (218 mg, 0.37 mmol) in dry ether (7 mL) at −78 °C. After stirring for 2 h, the reaction mixture was poured onto a vigorously stirred mixture of ether (40 mL) and 1.1 M aq. Rochelle's salt (40 mL) and stirred for a further 1 h. The layers were separated, and the aqueous layer extracted with ether (2 × 30 mL). The combined organic layers were then washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated.

The crude residue was dissolved in CH_2Cl_2 (7 mL), and acetic anhydride (76 mg, 0.74 mmol), triethylamine (52 mg, 0.52 mmol) and DMAP (6.4 mg, 0.05 mmol) were added. The resulting solution was stirred at RT for 2 h before being quenched with sat. aq. NH_4Cl (15 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and evaporated. The compound was either used directly in the next step without purification, or purified by flash chromatography (SiO_2, petrol/ether, 19:1→9:1, *v*/*v*) affording the *title compound* as a colourless oil (166 mg, 76% over two steps).

R_f 0.50 (ether/petrol, 2:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2933m, 2858m, 1738s, 1664w, 1586w, 1485w, 1428m, 1363m, 1229s, 1182m, 1150w, 1112s, 1055w, 1019w, 945w, 917w, 823w, 739w, 702s, 614m, 506m; ^{1}H NMR (400 MHz, C_6D_6) δ 7.74–7.69 (m, 4H), 7.18–7.13 (m, 6H), 6.97 (t, J = 7.8 Hz, 1H), 6.81 (t, J = 2.0 Hz, 1H), 6.78 (ddd, J = 8.1, 2.4, 1.0 Hz, 1H), 6.68 (dt, J = 7.7, 1.3 Hz, 1H), 4.78 (t, J = 8.1 Hz, 1H), 4.46 (d, J = 8.1 Hz, 2H), 3.72 (t, J = 6.9 Hz, 2H), 2.36 (tt, J = 6.9, 2.4 Hz, 2H), 2.30–2.20 (m, 4H), 1.95 (tt, J = 7.0, 2.4 Hz, 2H), 1.57 (s, 3H), 1.51–1.39 (m, 2H), 1.35–1.24 (m, 2H), 1.11 (s, 9H), 1.09 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 170.1, 164.0, 155.6, 144.7, 136.0, 134.1, 130.0, 129.8, 128.1, 124.5, 121.3, 118.5, 99.7, 81.4, 77.7, 63.4, 60.6, 35.5, 30.6, 28.8, 27.0, 23.4, 23.4, 20.6, 19.5, 19.0, 12.6; MS (ESI$^+$) *m*/*z* (rel. %) 605 ([M+Na]$^+$, 100), 621 ([M+K]$^+$, 5); HRMS (ESI$^+$) 605.3067 [M+Na]$^+$, $C_{37}H_{46}NaO_4Si$ requires 605.3058.

Lab book reference number: TOR-8-741

(*E*)-3-(3-[8-Hydroxyoct-5-ynyl]phenoxy)pent-2-enyl acetate (225)

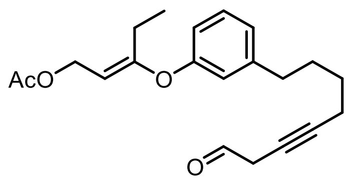


To a solution of silyl ether **224** (162 mg, 0.28 mmol) in dry THF (8 mL) was added TBAF (1 M in THF, 0.28 mL, 0.28 mmol), and the resulting solution stirred at RT for 2 h. At this point an additional portion of TBAF solution (0.03 mL, 0.03 mmol) was added and the reaction stirred for a further 30 min, before being diluted with ether (40 mL) and washed with sat. aq. NH_4Cl (20 mL). The layers were separated and the organic layer dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/EtOAc, 3:1, *v*/*v*) afforded the *title compound* as a colourless oil (78 mg, 80%).

R_f 0.13 (EtOAc/petrol, 1:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3443br, 2937m, 2860w, 1737s, 1664m, 1606w, 1585m, 1485m, 1442m, 1365m, 1303w, 1230s, 1181s, 1151m, 1053s, 1021s, 970m, 946m, 850w, 801m, 697m; ^{1}H NMR (400 MHz, C_6D_6) δ 7.04 (t, *J* = 7.8 Hz, 1H), 6.89 (t, *J* = 2.0 Hz, 1H), 6.85 (ddd, *J* = 8.1, 2.4, 1.0 Hz, 1H), 6.76 (dt, *J* = 7.6, 1.3 Hz, 1H), 4.84 (t, *J* = 8.1 Hz, 1H), 4.52 (d, *J* = 8.1 Hz, 2H), 3.43 (t, *J* = 6.5 Hz, 2H), 2.36–2.28 (m, 4H), 2.19 (tt, *J* = 6.6, 2.4 Hz, 2H), 1.99 (tt, *J* = 7.1, 2.4 Hz, 2H), 1.63 (s, 3H), 1.52 (tt, *J* = 9.2, 6.8 Hz, 2H), 1.39–1.27 (m, 2H), 1.15 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 170.3, 164.0, 155.6, 144.7, 129.8, 124.5, 121.3, 118.6, 99.7, 82.0, 77.5, 61.6, 60.6, 35.4, 30.6, 28.8, 23.6, 23.4, 20.6, 18.9, 12.6; MS (ESI$^+$) *m*/*z* (rel. %) 307 ([M−AcOH+Na]$^+$, 75), 367 ([M+Na]$^+$, 100), 383 ([M+K]$^+$, 10); HRMS (ESI$^+$) 367.1878 [M+Na]$^+$, $C_{21}H_{28}NaO_4$ requires 367.1880.

Lab book reference number: TOR-8-744

(*E*)-3-(3-[(8-formyl)oct-5-ynyl]phenoxy)pent-2-enyl acetate (208)



INITIAL REACTION: To a solution of alcohol **225** (29.2 mg, 0.085 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C was added $NaHCO_3$ (71.4 mg, 0.85 mmol) and Dess–Martin periodinane (108 mg, 0.25 mmol). The resulting suspension was stirred for 5 h at 0 °C before being quenched with sat. aq. $NaHCO_3$ (1.5 mL) and sat. aq. $Na_2S_2O_5$ (1.5 mL) and stirred for a further 5 min at 0 °C and 30 min at RT. The layers were separated, and the aqueous layer extracted with EtOAc (3 × 4 mL). The combined organic layers were washed with brine (4 mL), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether, 4:1, *v*/*v* → EtOAc) afforded the *title compound* as a colourless oil (13 mg, 45%).

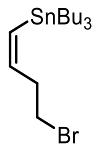
OPTIMISED PROCEDURE: To a solution of alcohol **225** (114 mg, 0.33 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C was added Dess–Martin periodinane (350 mg, 0.83 mmol). The resulting suspension was stirred for 5 min before the cooling was removed and the reaction stirred for a further 1.5 h at RT, after which time TLC analysis indicated that the reaction was complete. The solution was cooled to −15 °C, diluted with hexane (4 mL), and filtered through a short plug of silica, eluting with ether/pentane (4:1, *v*/*v*). The resulting clear solution was evaporated, affording the *title compound* as a colourless oil (97 mg, 86%).

R_f 0.49 (EtOAc/petrol, 2:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2939m, 2864w, 1735s, 1663w, 1604w, 1585w, 1485w, 1444w, 1365w, 1232s, 1182m, 1149w, 1052w, 1020m; ^{1}H NMR (400 MHz, C_6D_6) δ 9.07 (t, *J* = 1.7 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.90 (t, *J* = 2.0 Hz, 1H), 6.85 (ddd, *J* = 8.0, 2.4, 1.0 Hz, 1H), 6.79–6.75 (m, 1H), 4.85 (t, *J* = 8.0 Hz, 1H), 4.52 (d, *J* = 8.0 Hz, 2H), 2.58 (td, *J* = 2.4, 1.7 Hz, 2H), 2.35–2.28 (m, 4H), 1.95 (tt, *J* = 7.1, 2.4 Hz, 2H), 1.63 (s, 3H), 1.55–1.45 (m, 2H), 1.34–1.25 (m, 2H), 1.15 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 194.0, 170.1, 164.0, 155.7, 144.6, 129.8, 124.5, 121.2, 118.6, 99.8, 85.6, 71.3, 60.6, 35.4, 34.4, 30.5, 28.5, 23.4, 20.6, 18.8, 12.6; MS (ESI$^+$) *m*/*z* (rel. %) 397 ($[M+MeOH+Na]^+$, 100), 365 ($[M+Na]^+$, 45), 315 ($[M+MeOH-OAc]^+$, 10) 283 ($[M-OAc]^+$, 20); HRMS (ESI$^+$) 365.1739 $[M+Na]^+$, $C_{21}H_{26}NaO_4$ requires 365.1723.

Lab book reference number (initial reaction): TOR-7-643

Lab book reference number (optimised procedure): MV-1-047 (*reaction optimised by M. Völkel*)

(*Z*)-1-Tri-*n*-butylstannyl-4-bromobut-1-ene (226)



INITIAL REACTION: To a solution of 4-bromo-1-butyne (1.0 g, 7.52 mmol) in dry THF (50 mL) at −78 °C was added dropwise *n*-butyllithium (1.6 M in hexanes, 4.7 mL, 7.52 mmol), and the resulting solution was stirred for 10 min before dropwise addition of tributyltin chloride (2.69 g, 8.27 mmol). The cooling was removed and the reaction mixture stirred for 2.5 h at RT. The resulting solution was then diluted with ether (200 mL), washed with brine (100 mL), and water (100 mL), dried over Na_2SO_4, filtered and evaporated to afford a yellow oil which was used directly without further purification.

Diisobutylaluminium hydride (1.0 M in hexane, 9.02 mL, 9.02 mmol) was added dropwise to a solution of zirconocene dichloride (2.86 g, 9.78 mmol) in dry THF (20 mL) at 0 °C. The reaction mixture was then stirred for 1 h at 0 °C during which time an off-white suspension formed. A solution of the crude intermediate stannane (7.52 mmol) was then added in dry THF (5 mL), with additional dry THF (5 mL) used to rinse the flask and ensure quantitative transfer. The cooling was then removed, and the reaction mixture rapidly became a homogenous red solution. After stirring for 1.5 h, the reaction was quenched with water (2.7 mL) and diluted with *n*-pentane (40 mL), leading to the disappearance of the red colour and formation of a yellow solution containing a white precipitate. The reaction mixture was filtered through a Celite plug which was washed copiously with hexane. Evaporation of the filtrate and flash chromatography (SiO_2, petrol) afforded the *title compound* as a colourless oil (616 mg, 19% over two steps).

OPTIMISED PROCEDURE: To a solution of 4-bromo-1-butyne (2.87 g, 21.6 mmol) in dry THF (150 mL) at −78 °C was added dropwise *n*-butyllithium (2.0 M in hexanes, 10.65 mL, 21.6 mmol), and the resulting solution was stirred for 10 min before dropwise addition of tributyltin chloride (7.71 g, 23.7 mmol). The cooling was removed and the reaction mixture stirred for 1.5 h at RT. The resulting solution was then diluted with ether (50 mL), washed with brine (30 mL), and water (10 mL), dried over $MgSO_4$, filtered and evaporated to afford a yellow oil which was used directly without further purification.

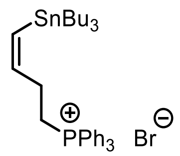
Diisobutylaluminium hydride (1.0 M in hexane, 26.5 mL, 26.5 mmol) was added dropwise to a solution of zirconocene dichloride (8.40 g, 28.7 mmol) in dry THF (50 mL) at 0 °C. The reaction mixture was then stirred for 10 min at 0 °C during which time an off-white suspension formed. A solution of the crude intermediate stannane (21.6 mmol) was then added in dry THF (10 mL), with additional dry THF (5 mL) used to rinse the flask and ensure quantitative transfer. The cooling was then removed, and the reaction mixture rapidly became a homogenous red solution. After stirring for 1 h, the reaction was diluted with *n*-pentane (60 mL) and quenched with water (1.2 mL), leading to the disappearance of the red colour and formation of a yellow solution containing a white precipitate. The reaction mixture was filtered through a Celite plug which was washed copiously with hexane. Evaporation of the filtrate and flash chromatography (SiO_2, petrol) afforded the *title compound* as a colourless oil (5.11 g, 55% over two steps).

R_f 0.43 (petrol); IR (thin film, cm^{-1}) ν_{max} 2957s, 2924s, 2871m, 2853m, 1599w, 1464m, 1418w, 1374w, 1340w, 1296w, 1264m, 1205w, 1072w, 1000w, 961w, 874w, 692m, 626w, 598w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (dt, J = 12.5, 6.9 Hz, $^3J_{^{119}Sn-H}$ = 135.9 Hz, $^3J_{^{117}Sn-H}$ = 130.0 Hz, 1H), 6.02 (dt, J = 12.5, 1.1 Hz, $^2J_{^{119}Sn-H}$ = 67.4 Hz, $^2J_{^{117}Sn-H}$ = 64.7 Hz, 1H), 3.38 (t, J = 7.2 Hz, 2H), 2.59 (qd, J = 7.1, 1.1 Hz, 2H), 1.54–1.44 (m, 6H), 1.37–1.25 (m, 6H), 0.96–0.90 (m, 6H), 0.89 (t, J = 7.3 Hz, 9H); ^{13}C NMR (101 MHz, C_6D_6) δ 144.9, 132.7, 40.0, 32.3, 29.3 ($^3J_{Sn-C}$ = 20.6 Hz), 27.5 ($^2J_{^{119}Sn-C}$ = 57.5 Hz, $^2J_{^{117}Sn-C}$ = 54.7 Hz), 13.9, 10.4 ($^1J_{^{119}Sn-C}$ = 341.4 Hz, $^1J_{^{117}Sn-C}$ = 326.7 Hz); MS (EI^+) m/z (rel. %) 423 ($[M-H]^+$, 100), 367 ($[M-Bu]^+$, 90), 311 ($[M-2Bu+H]^+$, 95), 255 ($[M-3Bu+2H]^+$, 50); HRMS (EI^+) 423.0701 $[M-H]^+$, $C_{16}H_{32}BrSn$ requires 423.0709.

Lab book reference numbers (initial reaction): TOR-7-605, TOR-7-606

Lab book reference numbers (optimised procedure): MV-1-064, MV-1-065 (*reactions optimised by M. Völkel*)

(*Z*)-4-Tri-*n*-butylstannylbut-3-enyl(triphenyl)phosphonium bromide (209)



INITIAL REACTION: A solution of stannane **226** (448 mg, 1.06 mmol) in dry MeCN (6 mL) was added to a Schlenk tube containing triphenylphosphine (415 mg, 1.58 mmol), and the resulting solution was stirred at 80 °C for 4 d, then 90 °C for 27 h. After this time an additional portion of triphenylphosphine (2.36 g, 9.01 mmol) was added and the reaction stirred at 90 °C for a further 24 h. The reaction mixture was then cooled to RT and the solvent removed *in vacuo*. The residue was dissolved in the minimum volume of CH_2Cl_2, *n*-pentane was then added, and the resulting precipitate collected by filtration and dried *in vacuo*, affording the *title compound* as a white solid (414 mg, 57%).

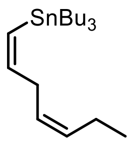
OPTIMISED PROCEDURE: A solution of stannane **226** (1.23 g, 2.9 mmol) in dry toluene/MeCN (1:1, 16 mL) was added to a Schlenk tube containing triphenylphosphine (3.80 g, 14.5 mmol) and NaI (43.5 mg, 0.29 mmol). The resulting solution was heated to 80 °C and stirred for 4 d. After this time, the reaction mixture was cooled to RT and the solvent removed *in vacuo*. The residue was taken up in pentane, and CH_2Cl_2 added until the slurry became a clear solution; *n*-pentane was then added, and the resulting precipitate collected by filtration and dried *in vacuo*, affording the *title compound* as a white solid (1.39 g, 70%).

M.P. 122 °C; R_f 0.18 (EtOAc/petrol, 1:1); IR (ATR, cm^{-1}) ν_{max} 2956m, 2922m, 2852m, 1587m, 1485m, 1436s, 1376w, 1317w, 1190w, 1111s, 1072m, 996m, 874w, 747s, 724s, 690s, 596m, 525s, 505s, 496s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.86 (m, 6H), 7.83–7.76 (m, 3H), 7.75–7.67 (m, 6H), 6.90 (dt, J = 12.8, 6.5 Hz, $^3J_{^{119}Sn-H}$ = 68.4 Hz, $^3J_{^{117}Sn-H}$ = 65.3 Hz, 1H), 5.92 (dt, J = 12.4, 1.2 Hz, $^2J_{Sn-H}$= 33.2 Hz, 1H), 4.07–3.93 (m, 2H), 2.37–2.25 (m, 2H). 1.36–1.25 (m, 6H), 1.23–1.10 (m, 6H), 0.81 (t, J = 7.2 Hz, 9H), 0.66–0.58 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3 (d, J_{C-P} = 17.8 Hz), 135.2 (d, J_{C-P} = 3.0 Hz), 133.9 (d, J_{C-P} = 10.0 Hz), 131.3 (d, J_{C-P} = 2.1 Hz), 130.7, (d, J_{C-P} = 12.6 Hz), 118.3 (d, J_{C-P} = 85.6 Hz), 29.6 (d, J_{C-P} = 3.7 Hz), 29.2 ($^3J_{Sn-C}$ = 20.5 Hz), 27.3 ($^2J_{Sn-C}$ = 55.3 Hz), 22.9 (d, J_{C-P} = 48.1 Hz), 13.8, 10.1 ($^1J_{^{119}Sn-C}$ = 340.5 Hz, $^1J_{^{117}Sn-C}$ = 323.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) 24.5; MS (ESI$^+$) m/z (rel. %) 607 ([M−Br]$^+$, 100); HRMS (ESI$^+$) 607.2533 [M−Br]$^+$, $C_{34}H_{48}PSn$ requires 607.2516.

Lab book reference number (initial reaction): TOR-7-620

Lab book reference number (optimised procedure): MV-1-035 (*reaction optimised by M. Völkel*)

(1*Z*,4*Z*)-1-Tri-*n*-butylstannylhepta-1,4-diene (227)

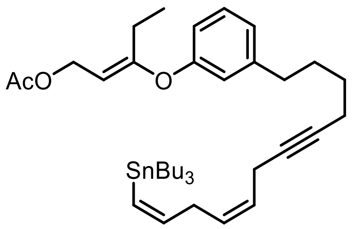


To a solution of phosphonium **209** (50.5 mg, 0.074 mmol) in dry THF (2 mL) was added NaHMDS (1 M in THF, 74 µL, 0.074 mmol) at −78 °C. The resulting bright yellow solution was stirred for 30 min, before propionaldehyde (5 µL, 0.067 mmol) was added and the cooling bath removed. After stirring for an additional 2 h at RT, the reaction mixture was diluted with EtOAc (5 mL), and water (5 mL). The layers were separated and the aqueous layer extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4,, filtered and evaporated. Purification by flash chromatography (SiO_2, hexane/triethylamine, 98:2, *v*/*v*) afforded the *title compound* as a colourless oil (24 mg, 93%).

IR (thin film, cm^{-1}) ν_{max} 2960m, 2925m, 2873w, 2854w, 1593w, 1464w, 1415w, 1259s, 1088s, 864m, 793s, 690m, 663m, 596w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (dt, J = 12.3, 7.0 Hz, $^3J_{^{119}Sn-H}$ = 141.5 Hz, $^3J_{^{117}Sn-H}$ = 135.2 Hz, 1H), 5.82 (dt, J = 12.3, 1.3 Hz, $^2J_{^{119}Sn-H}$ = 71.3 Hz, $^2J_{^{117}Sn-H}$ = 68.6 Hz, 1H), 5.41 (dtt, J = 10.7, 7.1, 1.6 Hz, 1H), 5.31 (dtt, J = 10.7, 7.1, 1.6 Hz, 1H), 2.78 (t, J = 7.1 Hz, 2H), 2.07 (app. quin, J = 7.4 Hz, 2H), 1.55–1.45 (m, 6H), 1.36–1.25 (m, 6H), 0.98 (t, J = 7.5 Hz, 3H), 0.97–0.86 (m, 6H), 0.89 (t, J = 7.3 Hz, 9H); ^{13}C NMR (101 MHz, C_6D_6) δ 147.3, 132.4, 128.6, 127.0, 35.1, 29.4 ($^3J_{Sn-C}$ = 20.1 Hz), 27.5 ($^2J_{^{119}Sn-C}$ = 56.9 Hz, $^2J_{^{117}Sn-C}$ = 54.7 Hz), 20.9, 14.4, 13.9, 10.4 ($^1J_{^{119}Sn-C}$ = 339.5 Hz, $^1J_{^{117}Sn-C}$ = 332.0 Hz).

Lab book reference number: TOR-7-618

(2*E*, 7*Z*, 10*Z*)-3-(3-[(12-tributylstannyl)dodeca-7,10-dien-5-ynyl]phenoxy)pent-2-enyl acetate (195)



INITIAL REACTION: To a solution of phosphonium salt **209** (208 mg, 0.30 mmol) in dry THF (1 mL) at −78 °C was added dropwise NaHMDS (1 M in THF, 0.23 mL, 0.23 mmol). The resulting orange solution was stirred for 45 min at −78 °C before a solution of aldehyde **208** (13.0 mg, 0.038 mmol) in dry THF (0.5 mL) was added *via* syringe. An additional portion of dry THF (0.5 mL) was used to ensure quantitative transfer. The resulting solution was stirred for 30 min before being warmed to 0 °C and stirred for 1 h. After this time, the reaction was quenched with water (3 mL) and EtOAc (3 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether/triethylamine, 88:10:2, *v*/*v*) afforded the *title compound* as a yellow oil (5.7 mg, 22%).

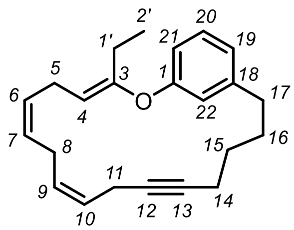
OPTIMISED PROCEDURE: To a solution of phosphonium salt **209** (410 mg, 0.60 mmol) in dry THF (1 mL) at −78 °C was added dropwise NaHMDS (1 M in THF, 0.57 mL, 0.57 mmol). The resulting orange solution was warmed to 0 °C for 10 min, before being cooled once again to −78 °C. A solution of aldehyde **208** (97 mg, 0.28 mmol) in dry THF (0.5 mL) was added *via* cannula. An additional portion of dry THF (1 mL) was used to ensure quantitative transfer. The resulting solution was warmed to RT and stirred for 3 h. After this time, the reaction was diluted with ether (4 mL) and quenched with water (2 mL) and brine (2 mL). The layers were separated and the aqueous layer extracted with ether (3 × 5 mL), and the combined organic layers dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether/triethylamine, 88:10:2, *v*/*v*) afforded the *title compound* as a yellow oil (81.7 mg, 43%).

R_f 0.32 (ether/petrol/triethylamine, 8:90:2, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2956m, 2926s, 2856m, 1739s, 1664w, 1586m, 1485w, 1464w, 1229s, 1182s, 1151w, 1055w, 1019m, 970w, 876w, 801w, 696m, 606w; ^{1}H NMR (400 MHz, C_6D_6) δ 7.04 (t, J = 7.8 Hz, 1H), 6.89 (t, J = 2.0 Hz, 1H), 6.85 (ddd, J = 8.0, 2.5, 1.0 Hz, 1H), 6.77 (dt, J = 7.7, 1.4 Hz, 1H), 6.56 (dt, J = 12.3, 1.2 Hz, 1H), 6.02 (dt, J = 12.3, 1.2 Hz, 1H), 5.62 (dtt, J = 10.2, 6.8, 1.6 Hz, 1H), 5.50 (dtt, J = 10.2, 7.0, 1.5 Hz, 1H), 4.84 (t, J = 8.1 Hz, 1H), 4.53 (d, J = 8.0 Hz, 2H), 3.00–2.94 (m, 2H), 2.88 (tt, J = 7.1, 1.4 Hz, 2H), 2.37–2.28 (m, 4H), 2.04 (tt, J = 7.1, 2.5 Hz, 2H), 1.64 (s, 3H), 1.63–1.50 (m, 8H), 1.43–1.32 (m, 8H), 1.16 (t, J = 7.5 Hz, 3H), 1.04–0.98 (m, 6H), 0.94 (t, J = 7.3 Hz, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.1, 163.9, 155.6, 146.9, 144.7, 129.8, 129.1, 129.0, 126.5, 124.5, 121.3, 118.5, 99.8, 80.3, 78.6, 60.6, 35.5, 35.4, 30.7, 29.7 ($^3J_{Sn-C}$ = 20.7 Hz), 28.9, 27.8 ($^2J_{Sn-C}$ = 54.4 Hz), 23.4, 20.6, 19.0, 17.9, 14.0, 12.6, 10.6 ($^1J_{^{119}Sn-C}$ = 339.5 Hz, $^1J_{^{117}Sn-C}$ = 323.9 Hz); ^{119}Sn NMR (186 MHz, C_6D_6) –60.6; MS (ESI$^+$) *m*/*z* (rel. %) 693 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 693.3276 [M+Na]$^+$, $C_{37}H_{58}NaO_3Sn$ requires 693.3307.

Lab book reference number (initial reaction): TOR-7-644

Lab book reference number (optimised procedure): MV-1-048 (*reaction optimised by M. Völkel*)

(3*E*,6*Z*,9*Z*)-3-Ethyl-2-oxabicyclo[16.3.1]docosa-1(22),3,6,9,18,20-hexaen-12-yne (91)



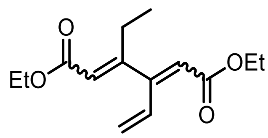
LiCl (15.1 mg, 0.36 mmol) was placed with a stirrer bar in a Schlenk tube and dried under vacuum with vigorous heating (approx. 10 min). Dry DMF (1.8 mL) was added and stirred until the LiCl had dissolved. The resulting solution was added *via* cannula to another Schlenk tube containing stannane **195** (24.0 mg, 35.8 μmol) and Pd(Br)(*N*-Succ)$(AsPh_3)_2$ (AsCat, 3.2 mg, 3.6 μmol). The resulting solution was stirred at 25 °C (controlled using an oil bath) for 72 h. After this time, the reaction mixture was diluted with ether (3 mL) and washed with water (4 × 3 mL). The combined aqueous layers were then re-extracted with ether (3 × 3 mL), and the combined organic layers washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated. Purification by preparatory thin layer chromatography (SiO_2, petrol/ether, 98:2, *v*/*v*) afforded the *title compound* as a colourless oil (5.0 mg, 44%).

R_f 0.49 (ether/petrol, 1:19, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3018w, 2933s, 2857m, 1743w, 1669w, 1602w, 1588m, 1485m, 1443m, 1249s, 1155s, 1048w, 989w, 799w, 696m; ^{1}H NMR (700 MHz, $CDCl_3$) 7.20 (t, *J* = 7.7 Hz, 1H, H-20), 6.83–6.81 (m, 3H, H-19, 21, 22), 5.48–5.43 (m, 2H, H-9, 10), 5.43–5.38 (m, 2H, H-6, 7), 4.62 (t, *J* = 7.6 Hz, 1H, H-4), 2.89 (dt, *J* = 5.8, 2.3 Hz, 2H, H-11), 2.86 (t, *J* = 5.6 Hz, 2H, H-8), 2.81–2.78 (m, 2H, H-5), 2.58 (t, *J* = 7.5 Hz, 2H, H-17), 2.34 (q, *J* = 7.5 Hz, 2H, H-1′), 2.16 (tt, *J* = 7.0, 2.3 Hz, 2H, H-14), 1.71–1.64 (m, 2H, H-16), 1.48–1.41 (m, 2H, H-15), 1.16 (t, *J* = 7.5 Hz, 3H, H-2′); ^{13}C NMR (175 MHz, $CDCl_3$) 156.7 (C, C-1 + C-3), 143.9 (C, C-18), 130.0 (CH, C-10), 129.6 (CH, C-20), 128.6 (CH, C-6), 128.0 (CH, C-7), 124.7 (CH, C-9), 123.2 (CH, C-19), 118.7 (CH, C-22), 117.5 (CH, C-21), 106.7 (CH, C-4), 79.9 (C, C-13), 78.4 (C, C-12), 35.4 (CH_2, C-17), 30.5 (CH_2, C-16), 28.0 (CH_2, C-15), 25.6 (CH_2, C-8), 24.9 (CH_2, C-5), 22.6 (CH_2, C-1′), 18.7 (CH_2, C-14), 17.2 (CH_2, C-11), 12.3 (CH_3, C-2′); MS ($APCI^+$) *m*/*z* (rel. %) 338 ($[M+NH_4]^+$, 100), 321 ($[M+H]^+$, 20); HRMS ($APCI^+$) 321.2237 $[M+H]^+$, $C_{23}H_{29}O$ requires 321.2213.

Lab book reference number: MV-1-055 (*reaction conducted by M. Völkel*)

See also: TOR-7-648

Diethyl 3-ethenyl-4-ethylhexa-2,4-dienedioate (236)

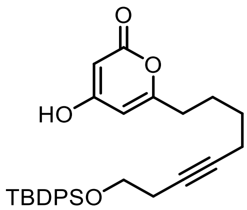


A flame-dried Schlenk tube containing a stirrer bar was charged with triflate (*E*)-**134** (200 mg, 0.72 mmol), 4-hydroxy-6-methyl-2-pyrone **36** (109 mg, 0.86 mmol) and K_3PO_4 (305 mg, 1.44 mmol) before being evacuated and backfilled with nitrogen. Dry toluene (4 mL) was added, followed by a premixed solution of $Pd(OAc)_2$ (3.3 mg, 0.014 mmol) and Q-Phos (15.3 mg, 0.022 mmol) in dry toluene (2 mL). Transfer was made quantitative with an additional portion of dry toluene (0.5 mL) and the reaction heated to 100 °C for 24 h. The reaction mixture was then filtered through amberlite and evaporated. Flash chromatography (SiO_2, petrol/ether, 95:5, *v*/*v*) afforded the *title compound* as a colourless oil (17 mg, 19%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 17.9, 11.0 Hz, 1H) 5.73 (s, 1H), 5.65 (s, 1H), 5.54 (dt, J = 10.7, 1.6 Hz, 1H), 5.44, (d, J = 17.9 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.19 (q, J = 7.2 Hz, 2H), 2.81 (q, J = 7.6 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.8, 161.2, 155.7, 131.8, 124.2, 119.5, 117.3, 60.4, 60.2, 30.4, 25.1, 14.3 (2 × CH_3, overlapping), 12.9; MS (ESI^+) m/z (rel. %) 253 ($[M+H]^+$, 60), 275 ($[M+Na]^+$, 100); HRMS (ESI^+) 275.1246 $[M+Na]^+$, $C_{14}H_{20}NaO_4$ requires 275.1254.

Lab book reference number: TOR-1-44

6-([8-*tert*-Butyldiphenylsilyl]oct-5-ynyl)-4-hydroxypyran-2-one (234)

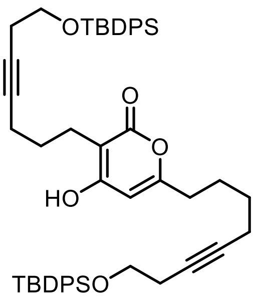


To a solution of 4-hydroxy-6-methyl-2-pyrone (100 mg, 0.79 mmol) in a Schlenk tube in dry THF (1 mL) and dry HMPA (0.42 mL) at −78 °C was added dropwise *n*-butyllithium (2.0 M in hexanes, 0.91 mL, 1.82 mmol). After 10 min, an additional portion of dry THF (1 mL) was added to aid stirring. After a further 15 min, a solution of iodide **222** (567 mg, 1.19 mmol) in dry THF (1 mL) was added dropwise, with an additional portion of THF (0.75 mL) used to ensure quantitative transfer. The resulting solution was stirred at −78 °C for 45 min, after which time the cooling was removed and the reaction immediately quenched with water (5 mL) and acidified to pH 1 with 3 M aq. HCl. The layers were separated, and the aqueous phase extracted with ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH, 19:1, *v*/*v*) afforded the *title compound* as a colourless oil (268 mg, 71%).

R_f 0.09 (EtOAc/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3072w, 2930s, 2859m, 1695m, 1663s, 1564s, 1428m, 1252m, 1111s, 824m, 738w, 702s, 614w, 505m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4H), 7.45–7.33 (m, 6H), 5.94 (d, J = 2.0 Hz, 1H), 5.56 (d, J = 2.0 Hz, 1H), 3.74 (t, J = 7.1 Hz, 2H), 2.51–2.41 (m, 2H), 2.41 (tt, J = 7.1, 2.3 Hz, 2H), 2.15 (tt, J = 7.0, 2.3 Hz, 2H), 1.77–1.66 (m, 2H), 1.55–1.43 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 168.0, 167.1, 135.7, 133.8, 129.8, 127.8, 101.4, 90.1, 80.6, 77.8, 63.0, 33.3, 28.2, 26.9, 25.9, 23.0, 19.4, 18.6; MS (ESI^+) m/z (rel. %) 475 ($[M+H]^+$, 70), 492 ($[M+NH_4]^+$, 100); HRMS (ESI^+) 475.2297 $[M+H]^+$, $C_{29}H_{35}O_4Si$ requires 475.2299.

Lab book reference number: TOR-10-912

3-([7-*tert*-Butyldiphenylsilyl]hept-4-ynyl)-6-([8-*tert*-butyldiphenylsilyl]oct-5-ynyl)-4-hydroxypyran-2-one (237)

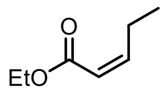


Title compound isolated as a byproduct from some syntheses of compound **234**.

IR (thin film, cm^{-1}) ν_{max} 3070w, 2955m, 2931m, 2857m, 1687m, 1624m, 1560m, 1472m, 1336w, 1256m, 1111s, 1008w, 823m, 738m, 702s, 614m, 505s, 490m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (br s, 1H), 7.69–7.65 (m, 12H), 7.46–7.30 (m, 18H), 5.58 (s, 1H), 3.78–3.76 (m, 4H), 2.49 (t, J = 7.7 Hz, 2H), 2.47–2.35 (m, 6H), 2.18–2.04 (m, 4H), 1.74–1.54 (m, 4H), 1.53–1.38 (m, 2H), 1.04 (2 × s, 2 × 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 166.4, 135.7 (2 × C), 133.9, 133.8, 129.8 (2 × C), 127.8 (2 × C), 105.4, 88.2, 87.9, 80.8, 80.7, 77.6, 60.0 (2 × C), 32.2, 28.7, 28.6, 27.0 (2 × C), 26.8, 26.7, 23.3, 23.0 (2 × C), 19.4 (2 × C), 18.6 (2 × C); MS (ESI$^+$) m/z (rel. %) 823 ([M+H]$^+$, 10) 845 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 845.4052 [M+Na]$^+$, $C_{52}H_{62}NaO_5Si_2$ requires 845.4028.

Lab book reference number: MV-1-057 (*reaction conducted by M. Völkel*)

Ethyl (*Z*)-2-pentenoate (239)[193]

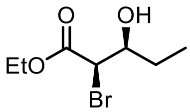


To a solution of ethyl 2-pentynoate (708 mg, 5.61 mmol) in THF/pyridine (15.4 mL, 10:1, *v*/*v*) was added Lindlar catalyst (120 mg, 17 wt%), and the reaction placed under an atmosphere of H_2 with vigorous stirring for 20 h at RT. After this time, the reaction mixture was filtered through Celite, eluting with ether (50 mL). The filtrate was washed with sat. aq. $CuSO_4$ (3 × 20 mL), dried over $MgSO_4$, filtered and evaporated. The crude residue was used directly in the next step; a small sample was purified to acquire analytical data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (dt, J = 11.5, 7.5 Hz, 1H), 5.73 (dt, J = 11.5, 1.7 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.65 (quind, J = 7.5, 1.7 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.05 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 152.1, 199.3, 59.9, 22.6, 14.4, 13.6.

Lab book reference number: TOR-9-742

Ethyl (2*R, 3*S**)-2-bromo-3-hydroxypentanoate (238)**

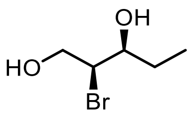


The crude (*Z*)-alkenoate **239** (38.8 mmol) was dissolved in MeCN/water (87 mL, 4:1, *v*/*v*), and *N*-bromosaccharin (15.2 g, 58.2 mmol) was added in one portion. The reaction mixture was stirred for 24 h at RT before being diluted with ether (250 mL), washed with sat. aq. $NaHCO_3$ (150 mL), sat. aq. $Na_2S_3O_3$ (150 mL) and water (150 mL), before being dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether, 4:1, *v*/*v*) afforded the *title compound* as a colourless oil (6.58 g, 64% over two steps).

R_f 0.40 (ether/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3490br, 2970m, 2938m, 1733s, 1464m, 1394w, 1371m, 1260s, 1206m, 1153s, 1115m, 1096m, 1052m, 1024s, 988m, 857w, 713w, 632w, 536m, 472m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (d, J = 4.2 Hz, 1H), 4.25 (qd, J = 7.1, 1.7 Hz, 2H), 3.82 (ddd, J = 7.8, 5.0, 4.2 Hz, 1H), 2.64 (br s, 1H), 1.64 (dt, J = 13.8, 7.5 Hz, 1H) 1.60–1.52 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 0.99 (t, J = 7.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 72.4, 62.5, 52.1, 27.4, 14.1, 10.0; MS (ESI$^+$) *m*/*z* (rel. %) 247 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 246.9934 [M+Na]$^+$, $C_7H_{13}BrNaO_3$ requires 246.9940.

Lab book reference number: TOR-9-763

(2*S, 3*S**)-2-Bromopentane-1,3-diol (240)**

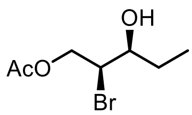


Ester **238** (2.0 g, 8.88 mmol) was dissolved in dry ether (40 mL) and cooled to 0 °C. Diisobutylaluminium hydride (1.0 M in hexanes, 28.2 mL, 28.2 mmol) was added dropwise over 20 min. The resulting solution was stirred for 6.5 h, before being diluted with ether (50 mL) and quenched with sat. aq. Rochelle's salt (60 mL). The biphasic mixture was stirred for 1 h, after which time the layers were separated, and the aqueous layer extracted with ether (3 × 40 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and evaporated. Crude reaction mixtures were generally used in the next step directly without purification; a small sample was purified to collect analytical data.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (td, J = 5.8, 2.4 Hz, 1H), 3.96 (t, J = 5.6 Hz, 2H), 3.66 (tdd, J = 7.8, 5.6, 2.4 Hz, 1H), 3.13 (t, J = 6.3 Hz, 1H), 2.56 (d, J = 7.6 Hz, 1H), 1.71–1.53 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 73.0, 65.4, 62.0, 28.9, 10.0; MS (ESI$^+$) m/z (rel. %) 205 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 204.9834 [M+H]$^+$, $C_5H_{11}BrNaO_2$ requires 204.9835.

Lab book reference number: TOR-9-769

(2*S, 3*S**)-2-Bromo-3-hydroxypentyl acetate (233)**

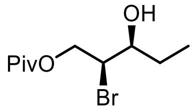


Crude diol **240** (8.88 mmol) and collidine (2.13 mL, 16.1 mmol) were dissolved in CH_2Cl_2 (30 mL) and cooled to −78 °C. Acetyl chloride (0.69 mL, 9.67 mmol) was added dropwise and the mixture allowed to slowly warm to RT. After 21 h, the reaction was quenched with 1 M aq. HCl (80 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether, 3:2, *v*/*v*) afforded the *title compound* as a colourless oil (1.14 g, 57% over two steps).

R_f 0.29 (ether/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3464br, 2968m, 2936m, 2880w, 1743s, 1459w, 1367m, 1234s, 1127w, 1081s, 1036m, 971w, 851w, 606w, 452w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (dd, J = 11.7, 7.6 Hz, 1H), 4.40 (dd, J = 11.6, 6.4 Hz, 1H), 4.19 (ddd, J = 7.6, 6.4, 2.3 Hz, 1H), 3.51 (ddd, J = 7.8, 5.4, 2.3 Hz, 1H), 2.10 (s, 3H), 1.75–1.63 (m, 1H), 1.63–1.53 (m, 1H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 71.6, 65.3, 57.2, 29.1, 21.0, 10.1; MS (ESI$^+$) m/z (rel. %) 247 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 246.9946 [M+Na]$^+$, $C_7H_{13}BrNaO_3$ requires 246.9940.

Lab book reference number: TOR-9-772

(2*S, 3*S**)-2-Bromo-3-hydroxypentyl pivalate (241)**

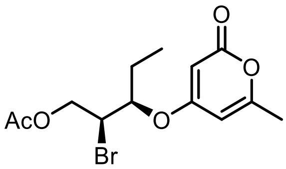


Crude diol **240** (11.24 mmol) was dissolved in CH_2Cl_2/pyridine (30 mL, 1:1, *v*/*v*) and cooled to 0 °C. Pivaloyl chloride (2.07 mL, 16.9 mmol) was added dropwise and the mixture stirred at 0 °C for 2 h. After this time, the reaction mixture was washed with water (60 mL) and sat. aq. $CuSO_4$ (2 × 60 mL). The combined aqueous layers were extracted with CH_2Cl_2 (60 mL), and the combined organic layers dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether, 7:3, *v*/*v*) afforded the *title compound* as a colourless oil (1.52 g, 51% over two steps).

R_f 0.39 (EtOAc/petrol, 1:4, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3474br, 2969m, 2936m, 2877w, 1732s, 1481m, 1461m, 1398w, 1367w, 1283s, 1154s, 1034w, 974w, 862w, 771w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (dd, *J* = 11.7, 7.3 Hz, 1H), 4.39 (dd, *J* = 11.7, 6.5 Hz, 1H), 4.20 (td, *J* = 6.9, 2.5 Hz, 1H), 3.49 (br m,1H), 1.95 (br m, 1H), 1.75–1.53 (m, 1H), 1.63–1.53 (m, 1H), 1.22 (s, 9H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.3, 71.8, 65.1, 57.5, 39.0, 28.9, 27.3, 10.1; MS (ESI^+) *m*/*z* (rel. %) 289 ($[M+Na]^+$, 100); HRMS (ESI^+) 289.0413 $[M+Na]^+$, $C_{10}H_{19}BrNaO_3$ requires 289.0410.

Lab book reference number: TOR-9-842

(2*S, 3*R**)-2-Bromo-3-(6-methyl-2-oxo-4-pyranyloxy)pentyl acetate (242)**



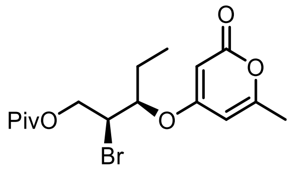
To a solution of acetate **233** (300 mg, 1.33 mmol), 4-hydroxy-6-methyl-2-pyrone **36** (84 mg, 0.66 mmol) and triphenylphosphine (350 mg, 1.33 mmol) in dry toluene (10 mL) at 40 °C was added DEAD (197 μL, 1.25 mmol). The resulting solution was stirred at 40 °C for 24 h, after which time it was cooled to RT and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc, 3:2, *v*/*v*) afforded the *title compound* as a colourless oil (100 mg, 45%).

R_f 0.34 (ether/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2974w, 1734s, 1650m, 1565s, 1450m, 1412w, 1243s, 1144w, 1038w, 1003w, 819w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dd, *J* = 2.3, 1.1 Hz, 1H), 5.41 (d, *J* = 2.2 Hz, 1H), 4.47 (q, *J* = 5.6 Hz, 1H), 4.41 (dd, *J* =

12.1, 5.4 Hz, 1H), 4.35 (dd, *J* = 12.1, 5.7 Hz, 1H), 4.28 (q, *J* = 5.6 Hz, 1H), 2.21 (d, *J* = 0.9 Hz, 3H), 2.10 (s, 3H), 1.95–1.85 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 169.6, 164.8, 162.9, 100.6, 88.6, 79.15, 64.4, 48.9, 24.3, 20.86, 20.0, 9.2; MS (ESI$^+$) *m*/*z* (rel. %) 355 ([M+Na]$^+$, 80), 333 ([M+H]$^+$, 100); HRMS (ESI$^+$) 333.0322 [M+H]$^+$, $C_{13}H_{18}BrO_5$ requires 333.0332.

Lab book reference number: TOR-9-791

(2*S, 3*R**)-2-Bromo-3-(6-methyl-2-oxo-4-pyranyloxy)pentyl pivalate (243)**

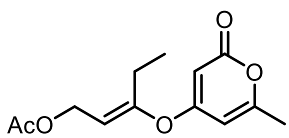


To a solution of pivalate **241** (175 mg, 0.655 mmol), 4-hydroxy-6-methyl-2-pyrone **36** (41.3 mg, 0.328 mmol) and triphenylphosphine (172 mg, 0.655 mmol) in toluene (6 mL) at −78 °C was added DEAD (103 µL, 0.655 mmol). The resulting solution was stirred at −78 °C for 40 min, then at RT for 40 min, after which time the solvent was removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc, 3:1, *v*/*v*) afforded the *title compound* as a colourless oil (81.6 mg, 66%).

R_f 0.10 (EtOAc/petrol, 1:4, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2973m, 1727s, 1650m, 1564s, 1480w,1449m, 1411w, 1319w, 1281m, 1242s, 1141s,1094w, 1036m, 1002m, 929w, 860w, 815w, 769w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (dd, *J* = 2.2, 1.0 Hz, 1H), 5.40 (d, *J* = 2.2 Hz, 1H), 4.50–4.40 (m, 2H), 4.35–4.28 (m, 2H), 2.21 (d, *J* = 1.0 Hz, 3H), 1.98–1.85 (m, 2H), 1.22 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 169.6, 164.7, 162.9, 100.6, 88.7, 79.2, 64.2, 49.1, 39.1, 27.3, 24.3, 20.0, 9.1; MS (ESI$^+$) *m*/*z* (rel. %) 397 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 397.0616 [M+Na]$^+$, $C_{16}H_{23}BrNaO_5$ requires 397.0621.

Lab book reference number: TOR-9-822

(*E*)-3-(6-Methyl-2-oxo-4-pyranyloxy)pent-2-enyl acetate (244)

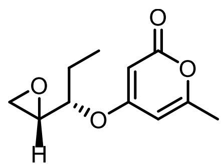


A solution of bromide **242** (22.3 mg, 0.067 mmol) and DBU (50.9 mg, 0.335 mmol) in dry dioxane (1.5 mL) was heated to 100 °C for 24 h. After this time, the reaction mixture was cooled to RT, diluted with CH_2Cl_2 (10 mL) and washed with sat. aq. NH_4Cl (2 × 10 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/EtOAc, 4:1, *v*/*v*) afforded the *title compound* as a colourless oil (2.8 mg, 17%).

R_f 0.32 (EtOAc/petrol, 2:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2925s, 1736s, 1647w, 1567m, 1448s, 1407w, 1376m, 1366m, 1228s, 1179w, 1139w, 1026m, 888w, 804m, 785w, 700w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (dd, *J* = 2.2, 1.0 Hz, 1H), 5.49 (d, *J* = 2.2 Hz, 1H), 5.33 (t, *J* = 7.8 Hz, 1H), 4.63 (d, *J* = 7.8 Hz, 2H), 2.36 (q, *J* = 7.5 Hz, 2H), 2.25–2.23 (m, 3H), 2.25–2.17, 2.08 (s, 3H), 1.08 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 169.3, 164.8, 163.4, 157.0, 112.2, 100.2, 91.0, 59.5, 22.3, 21.1, 20.2, 11.9; MS (ESI$^+$) *m*/*z* (rel. %) 375 ([M+Na]$^+$, 100), 253 ([M+H]$^+$, 25); HRMS (ESI$^+$) 275.0890 [M+Na]$^+$, $C_{13}H_{16}NaO_5$ requires 275.0890.

Lab book reference number: TOR-9-764

6-Methyl-4-[(1*S)-1-[(2*S**)-oxiran-2-yl]propoxy]-pyran-2-one (245)**



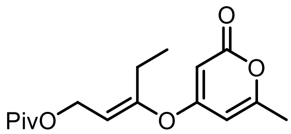
To a solution of bromide **242** (19.8 mg, 0.059 mmol) in dry THF (1 mL) was added KHMDS (0.7 M in toluene, 93 µL, 0.065 mmol) at 0 °C. The resulting red solution was stirred for 18 h at RT, before being quenched with NH_4Cl (10 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL); the combined organic layers were dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/EtOAc, 3:1, *v*/*v*) afforded the *title compound* as a colourless oil (3.0 mg, 24%, dr = 4:1).

NMR spectroscopic data given for the major diastereomer only.
R_f 0.19 (EtOAc/petrol, 2:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2972w, 2935w, 1715s, 1651s, 1563s, 1449m, 1409m, 1320w, 1244s, 1183w, 1145m, 1037m, 1002m, 928w, 860w, 815m, 660w, 548w; ^{1}H NMR (400 MHz, C_6D_6) δ 5.44 (d, *J* = 2.1 Hz, 1H), 5.20 (dd, *J* = 2.1, 1.0 Hz, 1H), 3.31 (qd, *J* = 6.2, 1.7 Hz, 1H), 2.56–2.47 (m, 1H), 2.16 (ddd, *J* = 5.1, 4.0, 1.1 Hz, 1H), 1.98 (ddd, *J* = 5.1, 2.5, 1.4 Hz, 1H), 1.45 (d, *J* = 1.0 Hz, 3H), 1.42–1.33 (m, 1H), 1.32–1.17 (m, 1H), 0.60 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) 169.2, 163.5, 162.3, 100.0, 89.4, 80.1, 52.4, 44.0, 24.5, 19.3, 9.4; MS (ESI$^+$) *m*/*z* (rel. %) 246 ([M+K]$^+$, 10), 233

([M+Na]$^+$, 100), 211 ([M+H]$^+$, 25); HRMS (ESI$^+$) 233.0775 [M+Na]$^+$, $C_{11}H_{14}NaO_4$ requires 233.0784.

Lab book reference number: TOR-8-756

(*E*)-3-(6-Methyl-2-oxo-4-pyranyloxy)pent-2-enyl pivalate (246)

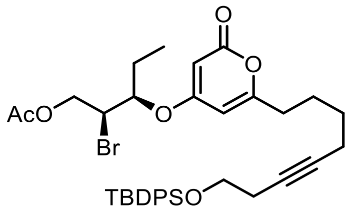


A solution of bromide **243** (22.7 mg, 0.061 mmol) and DBU (45 µL, 0.302 mmol) in dry toluene (1 mL) was heated to 100 °C for 22 h. After this time, the reaction mixture filtered through a short plug of silica, eluting with EtOAc. Evaporation of the filtrate and purification of the residue by flash chromatography (SiO_2, petrol/EtOAc, 4:1, *v*/*v*) afforded the *title compound* as a colourless oil (4.7 mg, 26%).

R_f 0.38 (EtOAc/petrol, 2:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2936m, 1732s, 1649w, 1567m, 1449w, 1407w, 1281w, 1229m, 1144s, 1033w, 821w; ^{1}H NMR (400 MHz, C_6D_6) δ 5.49 (d, *J* = 2.2 Hz, 1H), 5.24 (dd, *J* = 2.3, 1.1 Hz, 1H), 5.10 (t, *J* = 7.8 Hz, 1H), 4.30 (d, *J* = 7.8 Hz, 2H), 1.94 (q, *J* = 7.5 Hz, 2H), 1.46 (s, 3H), 1.16 (s, 9H), 0.82 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) 177.7, 168.7, 163.3, 163.1, 157.2, 112.5, 99.2, 91.2, 59.3, 38.8, 27.3, 22.2, 19.4, 11.7; MS (ESI$^+$) *m*/*z* (rel. %) 317 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 317.1360 [M+Na]$^+$, $C_{16}H_{22}NaO_5$ requires 317.1359.

Lab book reference number: TOR-9-826

(2*S, 3*R**)-2-Bromo-3-(6-([8-*tert*-Butyldiphenylsilyl]oct-5-ynyl)-2-oxo-4-pyranyloxy)pentyl acetate (232)**

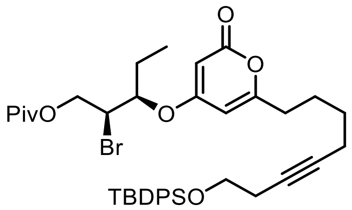


Diethylazodicarboxylate (60 mg, 0.35 mmol) was added dropwise to a solution of pyrone **234** (87 mg, 0.18 mmol), acetate **233** (83 mg, 0.37 mmol) and triphenylphosphine (96 mg, 0.37 mmol) in dry toluene (4 mL). The resulting solution was stirred for 24 h, before the solvent was removed in *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH, 99:1, *v*/*v*) afforded the *title compound* as a colourless oil (41.5 mg, 33%).

R_f 0.47 (EtOAc/petrol, 2:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2931m, 2858m, 1729s, 1647m, 1564m, 1462m, 1428m, 1370m, 1337w,1233s, 1104s, 1055m, 1009m, 917w, 822m, 740m, 703s, 614m, 505s, 491m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dt, *J* = 6.5, 1.6 Hz, 4H), 7.46–7.34 (m, 6H), 5.77 (d, *J* = 2.1 Hz, 1H), 5.41 (d, *J* = 2.1 Hz, 1H), 4.49–4.44 (m, 1H), 4.43–4.39 (m, 1H), 4.38–4.33 (m, 3H), 4.32–4.27 (m, 1H), 3.74 (t, *J* = 7.1 Hz, 2H), 2.48–2.38 (m, 4H), 2.21–2.14 (m, 2H), 2.11 (s, 3H), 1.97–1.85 (m, 2H), 1.73 (tt, *J* = 8.4, 7.3 Hz, 2H), 1.59–1.44 (m, 2H), 1.04 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 169.5, 166.3, 164.9, 135.7, 133.9, 129.8, 127.8, 100.0, 88.8,79.2, 77.8, 64.5, 63.0, 33.4, 28.3, 26.9, 25.8, 24.3, 23.0, 20.9, 19.4, 18.6, 9.2; MS (ESI$^+$) *m*/*z* (rel. %) 703 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 703.2063 [M+Na]$^+$, $C_{36}H_{45}BrNaO_6Si$ requires 703.2061.

Lab book reference number: TOR-9-778

(2*S, 3*R**)-2-Bromo-3-(6-([8-*tert*-Butyldiphenylsilyl]oct-5-ynyl)-2-oxo-4-pyranyloxy)pentyl pivalate (247)**

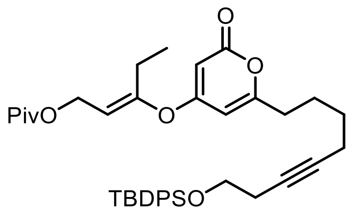


To a solution of pivalate **241** (194 mg, 0.728 mmol), pyrone **234** (173 mg, 0.364 mmol) and triphenylphosphine (191 mg, 0.728 mmol) in dry toluene (9 mL) at −78 °C was added DEAD (127 mg, 0.728 mmol). The resulting solution was stirred at −78 °C for 19 h, then at RT for 2 h, after which time the solvent was removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc, 9:1→4:1, *v*/*v*) afforded the *title compound* as a colourless oil (124 mg, 47%).

R_f 0.21 (EtOAc/petrol, 1:4, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2933m, 1733s, 1648m, 1565s, 1427m, 1239m, 1142s, 1112s, 822w, 739w, 703m, 614w, 506m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.63 (m, 4H), 7.46–7.32 (m, 6H), 5.77 (d, *J* = 2.0 Hz, 1H), 5.39 (d, *J* = 2.0 Hz, 1H), 4.50–4.41 (m, 2H), 4.35–4.29 (m, 2H), 3.74 (t, *J* = 7.1 Hz, 2H), 2.48–2.38 (m, 4H), 2.16 (tt, *J* = 7.0, 2.4 Hz, 2H), 1.98–1.86 (m, 2H), 1.80–1.67 (m, 2H), 1.54–1.47 (m, 2H), 1.23 (s, 9H), 1.04 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.87, 169.47, 166.20, 164.73, 135.66, 133.79, 129.73, 127.75, 99.95, 88.77, 80.61, 79.20, 77.73, 64.18, 62.93, 49.09, 39.01, 33.30, 28.29, 27.25, 26.88, 25.76, 24.21, 23.01, 19.31, 18.57, 9.13; MS (ESI$^+$) *m*/*z* (rel. %) 745 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 745.2512 [M+Na]$^+$, $C_{39}H_{51}BrNaO_6Si$ requires 745.2530.

Lab book reference number: TOR-10-859

(*E*)-3-(3-[8-*tert*-Butyldiphenylsilyloxyoct-5-ynyl]2-oxo-4-pyranyloxy)pent-2-enyl pivalate (248)

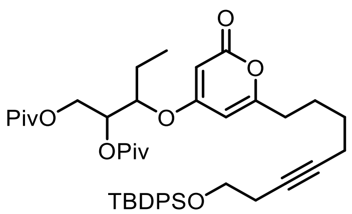


To a solution of bromide **247** (43.1 mg, 0.06 mmol) in dry toluene (1 mL) was added DBU (18.1 mg, 0.119 mmol), and the reaction heated to 100 °C for 3.5 d. After this time, the reaction mixture was cooled to RT and filtered through a short plug of silica, eluting with ether. Evaporation of the filtrate and purification by flash chromatography (SiO_2, petrol/ether, 9:1→1:1, *v*/*v*) afforded the *title compound* as a colourless oil (10.7 mg, 28%).

R_f 0.31 (EtOAc/petrol, 1:4, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2932m, 2858w, 1731s, 1645w, 1567m, 1462w, 1428m, 1280w, 1224m, 1143s, 1112s, 1052w, 823w, 703m, 614w, 505m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4H), 7.46–7.34 (m, 6H), 5.83 (d, *J* = 2.2 Hz, 1H), 5.45 (d, *J* = 2.2 Hz, 1H), 5.32 (t, *J* = 7.7 Hz, 1H), 4.62 (d, *J* = 7.7 Hz, 2H), 3.74 (t, *J* = 7.1 Hz, 2H), 2.49–2.40 (m, 4H), 2.37 (q, *J* = 7.6 Hz, 2H), 2.17 (tt, *J* = 7.1, 2.4 Hz, 2H), 1.79–1.69 (m, 2H), 1.54–1.47 (m, 2H), 1.20 (s, 9H), 1.07 (t, *J* = 7.6 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5, 169.3, 166.7, 164.8, 157.0, 135.7, 133.9, 129.8, 127.8, 112.5, 99.5, 91.1, 80.7, 77.8, 63.0, 59.4, 38.9, 33.5, 28.3, 27.3, 26.9, 25.9, 23.1, 22.4, 19.4, 18.6, 12.0; MS (ESI$^+$) *m*/*z* (rel. %) 665 ([M+Na]$^+$, 10), 660 ([M+NH_4]$^+$, 100), 643 ([M+H]$^+$, 10); HRMS (ESI$^+$) 665.3284 [M+Na]$^+$, $C_{39}H_{50}NaO_6Si$ requires 665.3269.

Lab book reference number: TOR-10-861

2-(Pivaloyloxy)-3-(6-[8-*tert*-Butyldiphenylsilyloxyoct-5-ynyl]-2-oxo-4-pyranyloxy)pentanyl pivalate (249)

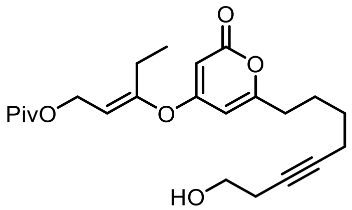


Title compound isolated as a byproduct in the synthesis of compound **248** (4.8 mg, 11%).

R_f 0.20 (EtOAc/petrol, 1:4, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2932m, 1732s, 1647w, 1565m, 1462w, 1428m, 1364w, 1239m, 1141s, 1111s, 912w, 821m, 736m, 702s, 619w, 506m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4H), 7.46–7.32 (m, 6H), 5.76 (d, *J* = 2.1 Hz, 1H), 5.48 (d, *J* = 2.1 Hz, 1H), 5.26 (td, *J* = 6.0, 3.7 Hz, 1H), 4.40 (dt, *J* = 7.2, 5.4 Hz, 1H), 4.31 (dd, *J* = 12.0, 3.7 Hz, 1H), 4.25–4.17 (m, 1H), 4.11 (dd, *J* = 12.0, 6.3 Hz, 1H), 3.74 (t, *J* = 7.1 Hz, 2H), 2.50–2.37 (m, 4H), 2.22–2.12 (m, 2H), 1.79–1.65 (m, 4H), 1.54–1.45 (m, 2H), 1.19 (s, 9H), 1.17 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 177.5, 170.1, 166.0, 165.0, 135.7, 133.9, 129.8, 127.8, 100.1, 88.6, 80.7, 78.1, 77.8, 70.7, 63.0, 62.3, 39.0, 33.3, 30.5, 28.3, 27.3, 27.2, 26.9, 25.9, 23.1, 22.9, 19.4, 18.6, 9.6, 1.2; MS (ESI$^+$) *m*/*z* (rel. %) 767 ([M+Na]$^+$, 10), 762 ([M+NH_4]$^+$, 100), 745 ([M+H]$^+$, 15); HRMS (ESI$^+$) 767.3949 [M+Na]$^+$, $C_{44}H_{60}NaO_8Si$ requires 767.3950.

Lab book reference number: TOR-10-861

(*E*)-3-(3-[8-Hydroxyoct-5-ynyl]2-oxo-4-pyranyloxy)pent-2-enyl pivalate (250)

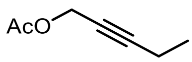


To a solution of silyl ether **249** (16.1 mg, 0.025 mmol) in dry THF (1 mL) was added dropwise TBAF (1 M in THF, 28 µL, 0.028 mmol). The resulting solution was stirred at RT for 50 min, before being diluted with ether (10 mL) and washed with sat. aq. NH_4Cl (10 mL). The aqueous phase was extracted with ether (2 × 10 mL), and the combined organic layers dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/EtOAc, 3:2, *v*/*v*) afforded the *title compound* as a colourless oil (4.5 mg, 45%).

R_f 0.28 (EtOAc/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3450br, 2925m, 1728s, 1642w, 1563m, 1417w, 1225m, 1146s, 1049m, 802w; ^{1}H NMR (400 MHz, $CDCl_3$) 5.87 (d, *J* = 2.2 Hz, 1H), 5.47 (d, *J* = 2.2 Hz, 1H), 5.34 (t, *J* = 7.7 Hz, 1H), 4.63 (d, *J* = 7.7 Hz, 2H), 3.69 (t, *J* = 6.2 Hz, 2H), 2.49 (t, *J* = 7.6 Hz, 2H), 2.43 (tt, *J* = 6.2, 2.4 Hz, 2H), 2.37 (q, *J* = 7.5 Hz, 2H), 2.22 (tt, *J* = 7.0, 2.4 Hz, 2H), 1.83–1.73 (m, 2H), 1.60–1.51 (m, 2H), 1.20 (s, 9H), 1.09 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5, 169.4, 166.6, 164.9, 157.1, 112.5, 99.6, 91.2, 81.7, 61.5, 59.4, 38.9, 33.5, 29.9, 28.2, 27.3, 25.9, 23.3, 22.4, 18.6, 12.0; MS (ESI$^+$) *m*/*z* (rel. %) 427 ([M+Na]$^+$, 100), 405 ([M+H]$^+$, 90); HRMS (ESI$^+$) 405.2286 [M+H]$^+$, $C_{23}H_{33}O_6$ requires 405.2272.

Lab book reference number: TOR-10-875

Pent-2-ynyl acetate (256)

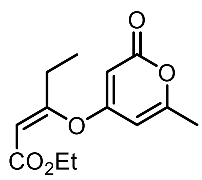


To a solution of 2-pentyn-1-ol (2.0 g, 23.8 mmol), triethylamine (3.37 g, 33.3 mmol) and DMAP (407 mg, 3.33 mmol) in CH_2Cl_2 (60 mL) was added dropwise acetic anhydride (4.86 g, 47.6 mmol), and the resulting solution stirred for 18 h at RT. After this time the reaction mixture was quenched with sat. aq. NH_4Cl (60 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with water (60 mL) and brine (60 mL), dried over $MgSO_4$, filtered and evaporated. The residue was purified by filtration through a short silica plug, eluting with CH_2Cl_2, followed by further washing with water (2 × 30 mL), drying over $MgSO_4$ and concentration *in vacuo* to afford the *title compound* as a slightly volatile colourless oil (2.45 g, 84%).

IR (thin film, cm^{-1}) ν_{max} 2980w, 2942w, 2242w, 1746s, 1438w, 1379m, 1224s, 1150w, 1025m, 972w, 913w, 831w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (t, J = 2.3 Hz, 2H), 2.24 (qt, J = 7.5, 2.3 Hz, 2H), 2.09 (s, 3H), 1.14 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 89.1, 73.3, 53.0, 21.0, 13.7, 12.6; MS (EI^+) m/z (rel. %) 126 ($[M]^+$, 2), 125 ($[M-H]^+$, 5), 111 ($[M-Me]^+$, 100), 97 ($[M-Et]^+$, 85); 84 ($[M-Ac+H]^+$, 95), 83 ($[M-Ac]^+$, 100); HRMS (ESI^+) 126.0681 $[M]^+$, $C_7H_{10}O_2$ requires 126.0681.

Lab book reference number: TOR-10-899

Ethyl (*Z*)-3-(6-Methyl-2-oxo-4-pyranyloxy)pent-2-enoate (257)

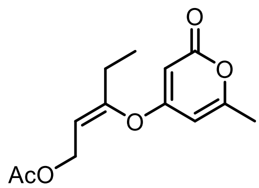


To a solution of ethyl 2-pentynoate (99 µL, 0.75 mmol) and 4-hydroxy-6-methyl-2-pyrone **36** (63.5 mg, 0.50 mmol) in toluene (1 mL) in a microwave vial at 110 °C was added $[(AuIPr)_2(\mu\text{-}OH)][BF_4]$ (6.4 mg, 0.005 mmol). The reaction was stirred for 20 h, before the solution was cooled to RT and evaporated. Purification of the crude residue with flash chromatography (SiO_2, EtOAc/petrol, 2:3, *v*/*v*) afforded the *title compound* as an orange oil (95.3 mg, 76%).

R_f 0.22 (EtOAc/petrol, 2:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3086vw, 2980w, 1716s, 1667m, 1646s, 1568s, 1448m, 1407m, 1369m, 1319m, 1278m, 1229s, 1191s, 1132s, 1036m, 1001m, 856m, 817m, 519w; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.95–5.94 (m, 1H), 5.67 (t, *J* = 1.2 Hz, 1H), 5.36 (dd, *J* = 2.3, 0.6 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.33 (qd, *J* = 7.4, 1.2 Hz, 2H), 2.24 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 168.7, 165.2, 164.8, 163.6, 163.2, 108.1, 99.8, 89.7, 60.6, 27.3, 20.2, 14.2, 10.6; MS (ESI$^+$) *m*/*z* (rel. %) 253 ([M+H]$^+$, 100), 275 ([M+Na]$^+$, 25), 181 ([M−CO_2Et+H]$^+$, 28); HRMS (ESI$^+$) 253.1065 [M+H]$^+$, $C_{13}H_{17}O_5$ requires 253.1071.

Lab book reference number: KE-1-45 (*reaction conducted by K. Evans*)

(*Z*)-3-(6-Methyl-2-oxo-4-pyranyloxy)pent-2-enyl acetate (258)

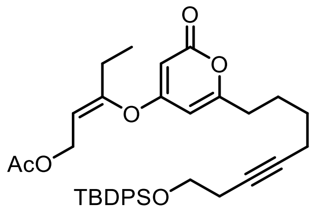


To a solution of pent-2-ynyl acetate **256** (91.6 mg, 0.75 mmol) and 4-hydroxy-6-methyl-2-pyrone (63.5 mg, 0.5 mmol) in toluene (1 mL) in a microwave vial at 80 °C was added $[(AuIPr)_2(\mu\text{-}OH)][BF_4]$ (3.2 mg, 0.0025 mmol). The reaction was stirred for 24 h, before the solution was cooled to RT and evaporated. Purification of the crude residue with flash chromatography (SiO_2, EtOAc/petrol, 2:3, *v*/*v*) afforded the *title compound* as a pale yellow oil (86.4 mg, 68%).

R_f 0.25 (EtOAc/petrol, 2:3, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2975w, 1729s, 1647m, 1567s, 1448m, 1407m, 1380m, 1365w, 1320w, 1223s, 1178m, 1137m, 1029m, 1008m, 858w, 822m, 521w; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89 (m, 1H), 5.41–5.33 (m, 2H), 4.48 (dt, *J* = 7.0, 1.1 Hz, 2H), 2.25–2.18 (m, 5H), 2.04 (s, 3H), 1.09 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.0, 168.7, 164.7, 163.6, 155.0, 111.5, 99.8, 90.1, 58.4, 25.4, 21.0, 20.2, 10.9; MS (ESI$^+$) *m*/*z* (rel.%) 275 ([M+Na]$^+$, 100), 253 ([M+H]$^+$, 2), 193 ([M−(AcOH)+H]$^+$, 14); HRMS (ESI$^+$) 275.0896 [M+Na]$^+$, $C_{13}H_{16}NaO_5$ requires 275.0890.

Lab book reference number: KE-1-57 (*reaction conducted by K. Evans*)

(*Z*)-3-(6-[8-*tert*-Butyldiphenylsilyloxyoct-5-ynyl]2-oxo-4-pyranyloxy)pent-2-enyl acetate (345)

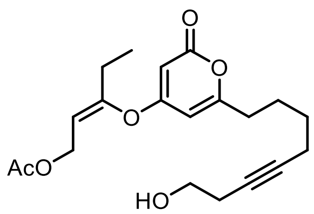


A solution of pyrone **234** (30 mg, 0.06 mmol), acetate **256** (39 mg, 0.32 mmol) and [(AuIPr)$_2$(μ-OH)][BF$_4$] (0.8 mg, 0.6 μmol) in toluene (0.5 mL) was heated to 110 °C and stirred for 5 h. Removal of the solvent *in vacuo* followed by flash chromatography (petrol/EtOAc, 4:1, *v*/*v*) afforded the *title compound* as a colourless oil (27.3 mg, 76%).

R_f 0.48 (EtOAc/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2932m, 2858m, 1733s, 1645m, 1568m, 1462w, 1428m, 1380w, 1221s, 1178w, 1111s, 1027w, 915w, 823m, 703s, 614m, 506m 491w; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70–7.65 (m, 4H), 7.45–7.35 (m, 6H), 5.86 (d, *J* = 2.2 Hz, 1H), 5.38 (d, *J* = 2.2 Hz, 1H), 5.37 (tt, *J* = 7.0, 1.3 Hz, 1H), 4.48 (dt, *J* = 7.0, 1.1 Hz, 2H), 3.74 (t, *J* = 7.1 Hz, 2H), 2.49–2.44 (m, 4H), 2.42 (tt, *J* = 7.2, 2.4 Hz, 2H), 2.25–2.20 (m, 2H), 2.17 (tt, *J* = 7.0, 2.4 Hz, 2H), 2.04 (s, 3H), 1.81–1.70 (m, 2H), 1.58–1.48 (m, 2H), 1.08 (t *J* = 7.4 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.0. 168.6, 166.9, 164.7, 155.0, 135.7, 133.8, 129.8, 127.8, 111.5, 99.2, 90.2, 80.6, 77.8, 63.0, 58.4, 33.4, 28.3, 26.9, 25.8, 25.3, 23.0, 21.0, 19.3, 18.6, 10.9; MS (ESI$^+$) *m*/*z* (rel. %) 623 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 623.2787 [M+Na]$^+$, $C_{36}H_{44}NaO_6Si$ requires 623.2799.

Lab book reference number: TOR-10-884

(*Z*)-3-(6-[8-Hydroxyoct-5-ynyl]2-oxo-4-pyranyloxy)pent-2-enyl acetate (259)

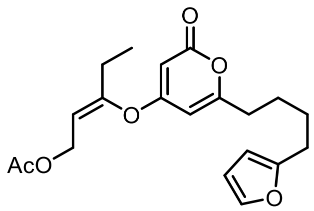


To a solution of silyl ether **343** (18.6 mg, 0.031 mmol) in dry THF (1 mL) at 0 °C was added TBAF (1 M in THF, 34 μL, 0.034 mmol) dropwise. The resulting solution was stirred at RT for 1.5 h, before being diluted with ether (10 mL) and washed with sat. aq. NH_4Cl (10 mL). The aqueous layer was extracted with ether (2 × 10 mL), and the combined organic layers dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (petrol/EtOAc, 1:1, *v*/*v*) afforded the *title compound* as a colourless oil (10.0 mg, 89%).

R_f 0.20 (EtOAc/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3443br, 2936m, 1727s, 1643m, 1565s, 1417m, 1380m, 1365w, 1222s, 1179m, 1136w, 1031m, 960w, 824m, 607w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, *J* = 2.2 Hz, 1H), 5.39 (d, *J* = 2.2 Hz, 1H), 5.37 (tt, *J* = 7.0, 1.3 Hz, 1H), 4.48 (d, *J* = 7.0 Hz, 2H), 3.69 (t, *J* = 6.2 Hz, 2H), 2.50 (t, *J* = 7.6 Hz, 2H), 2.43 (tt, *J* = 6.2, 2.4 Hz, 2H), 2.27–2.17 (m, 4H), 2.04 (s, 3H), 1.85–1.73 (m, 2H), 1.63–1.49 (m, 2H), 1.09 (t *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0. 168.6, 166.9, 164.7, 155.0, 111.5, 99.3, 90.3, 81.7, 77.5, 61.5, 58.5, 33.5, 28.2, 25.8, 25.4, 23.3, 21.0, 18.6, 10.9; MS (ESI$^+$) *m*/*z* (rel. %) 385 ([M+Na]$^+$, 100), 363 ([M+H]$^+$, 5); HRMS (ESI$^+$) 385.1611 [M+Na]$^+$, $C_{20}H_{26}NaO_6$ requires 385.1622.

Lab book reference number: TOR-10-891

(*Z*)-3-(6-[4-(Furan-2-yl)butyl]2-oxo-4-pyranyloxy)pent-2-enyl acetate (261)

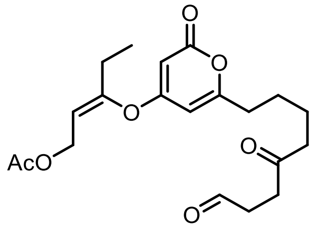


Title compound was isolated as a side product from some oxidations of compound **259** (when not purified with Quadrapure) (6.8 mg, 17%).

R_f 0.37 (EtOAc/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2929m, 1806w, 1738s, 1645m, 1568s, 1462w, 1417m, 1379w, 1222s, 1177w, 1136w, 1019m, 822w; ^{1}H NMR (400 MHz, C_6D_6) δ 7.12 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.12 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.83 (dt, *J* = 3.0,0.9 Hz, 1H), 5.41 (d, *J* = 2.3 Hz, 1H), 5.37 (d, *J* = 2.3 Hz, 1H), 5.00 (tt, *J* = 7.1, 1.3 Hz, 1H), 4.43 (dt, *J* = 7.1, 1.3 Hz, 2H), 2.32 (t, *J* = 7.2 Hz, 2H), 1.88–1.80 (m, 2H), 1.70 (qd, *J* = 7.5, 1.3 Hz, 2H), 1.64 (s, 3H), 1.47–1.31 (m, 2H), 1.27–1.17 (m, 2H), 0.66 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.0, 168.1, 167.1, 163.3, 156.0, 155.0, 141.2, 111.9, 110.6, 105.5, 98.4, 90.6, 58.1, 33.6, 27.8, 27.7, 26.1, 25.1, 20.3, 10.8; MS (ESI$^+$) *m*/*z* (rel. %) 383 ([M+Na]$^+$, 100), 361 ([M+H]$^+$, 5); HRMS (ESI$^+$) 383.1461 [M+Na]$^+$, $C_{20}H_{24}NaO_6$ requires 383.1465.

Lab book reference number: TOR-10-911

(*Z*)-3-(6-[5,8-Dioxooctyl]2-oxo-4-pyranyloxy)pent-2-enyl acetate (262)

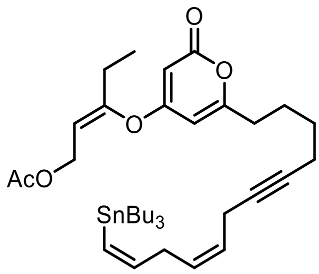


Alcohol **259** (8.9 mg, 0.025 mmol, not purified with Quadrapure) was dissolved in dry CH_2Cl_2 (2 mL), and Celite (10 mg) and PCC (8.0 mg, 0.037 mmol) were added sequentially at 0 °C. The resulting solution was stirred at this temperature for 45 min, before being warmed to RT and stirred for another 2.5 h. After this time, the solution was filtered through as short plug of silica and flushed with EtOAc. The eluent was evaporated, and the crude residue purified by flash chromatography (EtOAc/petrol, 2:3, *v*/*v*), affording the *title compound* as a colourless oil (5.4 mg, 57%).

R_f 0.65 (EtOAc); IR (thin film, cm^{-1}) ν_{max} 2930m, 1721br s, 1644m, 1567s, 1461w, 1417m, 1380w, 1365w, 1222s, 1176w, 1135w, 1025w, 822w; ^1H NMR (400 MHz, C_6D_6) δ 9.25 (s, 1H), 5.45 (d, *J* = 2.2 Hz, 1H), 5.43 (d, *J* = 2.2 Hz, 1H), 5.01 (tt, *J* = 7.0, 1.3 Hz, 1H), 4.44 (dt, *J* = 7.1, 1.1 Hz, 2H), 2.09 (ddd, *J* = 6.7, 5.0, 1.4 Hz, 2H), 2.06–2.00 (m, 2H), 1.90–1.85 (t, *J* = 7.0 Hz, 2H), 1.82 (t, *J* = 7.0 Hz, 2H), 1.71 (qq, *J* = 7.4, 1.1 Hz, 2H), 1.64 (s, 3H), 1.34–1.24 (m, 2H), 1.28–1.13 (m, 2H), 0.67 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 199.2, 170.0, 168.2, 166.9, 163.3, 155.0, 111.9, 98.6, 90.6, 58.1, 41.8, 37.5, 34.5, 33.6, 26.1, 25.2, 23.1, 20.3, 10.7; MS (ESI^+) *m/z* (rel. %) 401 ($[M+Na]^+$, 100), 385 ($[M+H]^+$, 10); HRMS (ESI^+) 401.1565 $[M+Na]^+$, $C_{20}H_{26}NaO_7$ requires 401.1571.

Lab book reference number: TOR-10-918

(2Z,7Z,10Z)-3-(6-[(12-tributylstannyl)dodeca-7,10-dien-5-ynyl]2-oxo-4-pyranyloxy)pent-2-enyl acetate (263)



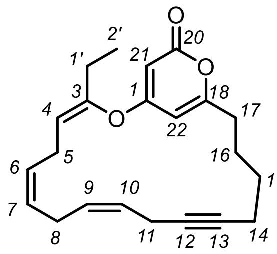
To a solution of alcohol **259** (49.2 mg, 0.14 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C was added Dess–Martin periodinane (86 mg, 0.20 mmol). The resulting suspension was stirred for 5 min before the cooling was removed and the reaction stirred for a further 1 h at RT, after which time TLC analysis indicated that the reaction was complete. The solution was cooled to −10 °C, diluted with pentane (2 mL), and filtered through a short plug of layered silica and Celite, eluting successively with ether/petrol (1:1, *v*/*v*), CH_2Cl_2 and EtOAc/petrol (1:1, *v*/*v*). The resulting solution was evaporated, and the crude residue triturated with ether, decanted and evaporated, affording a crude residue which was used directly in the next step.

To a solution of phosphonium salt **209** (196 mg, 0.29 mmol) in dry THF (0.5 mL) at −78 °C was added dropwise NaHMDS (1 M in THF, 0.27 mL, 0.27 mmol). The resulting orange solution was warmed to 0 °C for 10 min, before being cooled once again to −78 °C. A solution of the crude aldehyde (0.14 mmol) in dry THF (0.5 mL) was added, and an additional portion of dry THF (0.5 mL) was used to ensure quantitative transfer. The resulting solution was warmed to RT and stirred for 1 h. After this time, the reaction was diluted with ether (4 mL) and quenched with water (2 mL) and brine (2 mL). The layers were separated and the aqueous layer extracted with ether (3 × 5 mL), and the combined organic layers dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (SiO_2, petrol/ether/triethylamine, 83:15:2, *v*/*v*) afforded the *title compound* as a yellow oil (13.3 mg, 14%).

R_f 0.32 (EtOAc/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2956m, 2926s, 2871w, 2854w, 1740s, 1646m, 1570m, 1463w, 1416w, 1364w, 1221s, 1177w, 1134w, 1023w, 822w, 692w; ^1H NMR (500 MHz, C_6D_6) δ 6.56 (dt, *J* = 12.3, 7.0 Hz, 1H), 6.02 (d, *J* = 12.3 Hz, 1H), 5.67–5.57 (m, 1H), 5.56–5.46 (m, 1H), 5.47–5.39 (m, 2H), 5.01 (t, *J* 7.1 Hz, 1H), 4.44 (d, *J* = 7.1 Hz, 2H), 2.97 (dd, *J* = 7.0 Hz, 2.1 Hz, 2H), 2.89 (t, *J* = 7.0 Hz, 2H), 1.95 (tt, *J* = 7.1, 2.1 Hz, 2H), 1.90 (t, *J* = 7.7 Hz, 2H), 1.72 (q, *J* = 7.5 Hz, 2H), 1.65 (s, 3H), 1.64–1.54 (m, 6H), 1.44–1.32 (m, 6H), 1.20–1.26 (m, 2H), 1.12–1.03 (m, 2H), 1.05–0.99 (m, 6H), 0.94 (t, *J* = 7.3 Hz, 9H), 0.68 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 169.9, 168.0, 167.0, 163.1, 155.0, 146.8, 129.2, 129.1, 126.3, 111.8, 98.4, 90.5, 79.9, 78.9, 58.1, 35.4, 33.4, 30.5, 29.7, 28.5, 27.8, 25.8, 25.2, 20.3, 18.8, 17.9, 14.0, 10.6; MS (ESI^+) *m*/*z* (rel. %) 711 ($[M+Na]^+$, 100); HRMS (ESI^+) 711.3070 $[M+Na]^+$, $C_{36}H_{56}NaO_5Sn$ requires 711.3049.

Lab book reference number: TOR-10-929

(3*Z*,6*Z*,9*Z*)-3-Ethyl-2,19-dioxabicyclo[16.3.1]docosa-1(21),3,6,9,18-pentaen-12-yn-20-one (264)

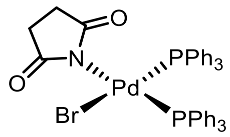


LiCl (8.0 mg, 0.19 mmol) was placed with a stirrer bar in a Schlenk tube and dried under vacuum with vigorous heating (approx. 10 min). Dry DMF (1.0 mL) was added and stirred until the LiCl had dissolved. The resulting solution was added *via* cannula to another Schlenk tube containing stannane **263** (13.3 mg, 19.3 μmol) and Pd(Br)(*N*-Succ)($AsPh_3$)$_2$ (AsCat, 1.7 mg, 1.9 μmol). The resulting solution was stirred at 35 °C for 18 h. After this time, the reaction mixture was diluted with ether (10 mL) and washed with water (3 × 5 mL). The combined organics layers were dried over $MgSO_4$, filtered and evaporated. Purification by preparatory thin layer chromatography (SiO_2, petrol/EtOAc, 1:1, *v*/*v*) afforded the *title compound* as a yellow oil (1.3 mg, 20%).

R_f 0.58 (EtOAc/petrol, 1:1, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2925s, 2854m, 1733s, 1645m, 1567m, 1462w, 1417w, 1223m, 1131w, 821w, 702w; ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.03 (d, *J* = 2.2 Hz, 1H, H-22), 5.54–5.47 (m, 1H, H-10), 5.42 (d, *J* = 2.2 Hz, 1H, H-21), 5.41–5.34 (m, 3H, H-6, 7, 9), 5.16 (t, *J* = 7.3 Hz, H-4), 2.87 (d, *J* 7.5 Hz, 2H, H-11), 2.81 (t, *J* = 7.5 Hz, 2H, H-8), 2.66 (t, *J* = 7.3 Hz, 2H, H-5), 2.51 (t, *J* = 6.9 Hz, 2H, H-17), 2.23–2.16 (m, 4H, H-14, 1′), 1.81 (app. quin, *J* = 6.9 Hz, 2H, H-16), 1.62–1.53 (m, 2H, H-15), 1.07 (t, *J* = 7.4 Hz, 3H, H-2′); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.2 (C, C-20), 167.1 (C, C-18), 165.3 (C, C-1), 151.3 (C, C-3), 130.8 (CH, C-9), 128.6 (CH, C-7), 126.9 (CH, C-6), 124.6 (CH, C-10), 114.4 (CH, C-4), 99.2 (CH, C-22), 89.8 (CH, C-21), 79.5 (C, C-13), 79.2 (C, C-12), 32.5 (CH_2, C-17), 27.5 (CH_2, C-16), 25.7 (CH_2, C-1′), 25.5 (CH_2, C-8), 25.2 (CH_2, C-15), 23.9 (CH_2, C-5), 18.3 (CH_2, C-14), 17.0 (CH_2, C-11), 11.2 (CH_3, C-2′); MS (ESI$^+$) *m*/*z* (rel. %) 361 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 361.1761 [M+Na]$^+$, $C_{22}H_{26}NaO_3$ requires 361.1774.

Lab book reference number: TOR-10-931

cis-Bromobis(triphenylphosphine)(_N_-succinimide)palladium(II) (_cis_-23)[53]

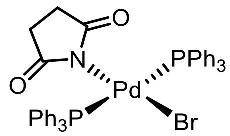


Prepared using general procedure A (L = PPh_3), affording the *title compound* as a yellow powder (48 mg, 31%).

M.P. 234–237 °C (dec.); IR (CH_2Cl_2, cm^{-1}) ν_{max} 1632s, 1437m, 1355m, 1243w, 1097m; ^1H NMR (400 MHz, CD_2Cl_2) δ 7.70–7.62 (m, 6H), 7.45–7.38 (m, 3H), 7.35 (dd, J = 9.7, 7.3 Hz, 9H, overlapping), 7.27 (td, J = 7.7, 2.2 Hz, 6H), 7.22–7.14 (m, 6H), 2.24–2.16 (m, 2H), 1.62–1.55 (m, 2H); ^{31}P NMR (162 MHz, CD_2Cl_2) δ 33.6 (d, J = 8.8 Hz), 24.0 (d, J = 8.8 Hz); UV–Vis (CH_2Cl_2, nm) λ_{max} 280 (ε = 30960).

Lab book reference number: TOR-4-344

trans-Bromobis(triphenylphosphine)(_N_-succinimide)palladium(II) (_trans_-23)[284]



Compound was obtained commercially from Sigma-Aldrich. No published data is available.

M.P. 220–225 °C (dec.); IR (ATR, cm^{-1}) ν_{max} 1634s, 1481w, 1433m, 1351w, 1235s, 1098s, 744s, 691s; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78–7.75 (m, 12H), 7.51–7.42 (m, 18H), 1.65 (s, 2H), 1.28 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.6, 135.1 (vt, $\Sigma\ ^{2/3}J_{C\text{–}P} + {}^{4/5}J_{C\text{–}P}$ = 13.0 Hz), 130.7 (vt, $\Sigma\ ^{4}J_{C\text{–}P} + {}^{6}J_{C\text{–}P}$ = 1.9 Hz), 130.5 (vt, $\Sigma\ ^{1}J_{C\text{–}P} + {}^{3}J_{C\text{–}P}$ = 49.1 Hz), 128.3 (vt, $\Sigma\ ^{2/3}J_{C\text{–}P} + {}^{4/5}J_{C\text{–}P}$ = 10.7 Hz), 30.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.4.

Ethyl 3-(tributylstannyl)propenoates (278)[222]

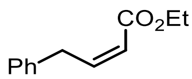
AIBN (67 mg, 0.41 mmol) was added to a neat mixture of ethyl propiolate (1.0 g, 10.2 mmol) and tributyltin hydride (3.12 g, 10.7 mmol), and the mixture heated to 60 °C for 2 h. It was then allowed to cool to RT and purified by flash chromatography (SiO_2, petrol/EtOAc, 95:5, *v*/*v*), affording the *E*-isomer (600 mg, 15%) and the *Z*-isomer (1.92 g, 48%), both as colourless oils.

Z-isomer: R_f 0.65 (ether/petrol, 1:9, *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 12.9 Hz, $^2J_{^{119}Sn-H}$ = 59.1 Hz, $^2J_{^{117}Sn-H}$ = 56.4 Hz, 1H), 6.72 (d, J = 12.9 Hz, $^3J_{^{119}Sn-H}$ = 114.2 Hz, $^3J_{^{117}Sn-H}$ = 109.3 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.57–1.37 (m, 6H), 1.34–1.23 (m, 9H), 1.05–0.88 (m, 6H), 0.87 (t, J = 7.3, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 157.2, 135.5, 60.6, 29.3 ($^3J_{Sn-C}$ = 21.0 Hz), 27.5 ($^2J_{^{119}Sn-C}$ = 58.2 Hz, $^2J_{^{117}Sn-C}$ = 55.7 Hz), 14.4, 13.9 ($^4J_{Sn-C}$ = 1.0 Hz), 11.2 ($^1J_{^{119}Sn-C}$ = 361.8 Hz, $^1J_{^{117}Sn-C}$ = 346.4 Hz); MS (ESI$^+$) *m*/*z* (rel. %) 413 ([M+Na]$^+$, 100); HRMS (ESI$^+$) 413.1488 [M+Na]$^+$, $C_{17}H_{34}NaO_2Sn$ requires 413.1476.

E-isomer: R_f 0.53 (ether/petrol, 1:9, *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 19.4 Hz, $^2J_{^{119}Sn-H}$ = 61.0 Hz, $^2J_{^{117}Sn-H}$ = 58.4 Hz, 1H), 6.30 (d, J = 19.4 Hz, $^3J_{^{119}Sn-H}$ = 54.9 Hz, $^3J_{^{117}Sn-H}$ = 52.6 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.61–1.40 (m, 6H), 1.36–1.25 (m, 9H), 1.06–1.89 (m, 6H), 0.87 (t, J = 7.3, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 152.6, 136.5, 60.5, 29.1 ($^3J_{Sn-C}$ = 21.4 Hz), 27.4 ($^2J_{^{119}Sn-C}$ = 57.3 Hz, $^2J_{^{117}Sn-C}$ = 54.5 Hz), 14.4, 13.8, 9.8 ($^1J_{^{119}Sn-C}$ = 349.9 Hz, $^1J_{^{117}Sn-C}$ = 334.8 Hz); MS (ESI$^+$) *m*/*z* (rel. %) 413 ([M+Na]$^+$, 100); 391 ([M+H]$^+$, 20) HRMS (ESI$^+$) 413.1469 [M+Na]$^+$, $C_{17}H_{34}NaO_2Sn$ requires 413.1476.

Lab book reference number: TOR-5-398

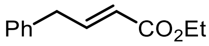
Ethyl (*Z*)-4-phenyl-2-butenoate (*Z*-281)[208]



Title compound was synthesised using general procedure B as a colourless oil.

R_f 0.51 (ether/petrol, 1:9, *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 2H), 7.25–7.19 (m, 3H), 6.35 (dt, J = 11.4, 7.6 Hz, 1H), 5.35 (dt, J = 11.4, 1.8 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.03 (dd, J = 7.6, 1.8 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 148.1, 139.6, 128.8 (2 × CH, overlapping), 126.5, 120.1, 60.2, 35.3, 14.4; MS (ESI$^+$) *m*/*z* (rel. %) 213 ([M+Na]$^+$, 100), 191 ([M+Na]$^+$, 60); HRMS (ESI$^+$) 213.0880 [M+Na]$^+$, $C_{12}H_{14}NaO_2$ requires 213.0886.

Ethyl (*E*)-4-phenyl-2-butenoate (*E*-281)[208]



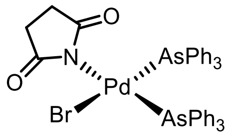
Title compound was synthesised using general procedure B as a colourless oil.

R_f 0.30 (ether/petrol, 1:9, *v*/*v*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 2H), 7.27–7.21 (m, 1H), 7.18 (ddt, *J* = 7.4, 1.3, 0,6 Hz, 2H), 7.10 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.81 (dt, *J* = 15.61.7 Hz, 1H) 4.18 (q, *J* = 7.1 Hz, 2H), 3.52 (dd, *J* = 6.8, 1.7 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 147.4, 137.9, 129.0, 126.8, 122.5, 60.4, 38.6, 14.4; MS (ESI$^+$) *m*/*z* (rel. %) 213 ([M+Na]$^+$, 100), 191 ([M+Na]$^+$, 50); HRMS (ESI$^+$) 213.0883 [M+Na]$^+$, $C_{12}H_{14}NaO_2$ requires 213.0886.

DMF-stabilised palladium nanoparticles

To a round-bottomed flask equipped with a reflux condenser containing dry DMF (15 mL) at 140 °C under air was added a suspension of $PdCl_2$ in H_2O (0.1 M, 150 μL, 0.015 mmol). The resulting solution was stirred for 6 h at 140 °C, before being cooled and stored at 5 °C. Aliquots of the 1 mM solution were used directly in the relevant reactions.

***cis*-Bromobis(triphenylarsine)(*N*-succinimide)palladium(II) (229)**



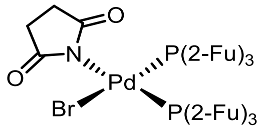
Prepared using general procedure A (L = $AsPh_3$), affording the *title compound* as a light brown powder (179.5 mg, 52%). Single crystals were grown by vapour diffusion of pentane into a saturated solution of the compound in CH_2Cl_2.

M.P. 108–112 °C (dec.); IR (ATR, cm^{-1}) ν_{max} 1715w, 1637s, 1482w, 1436m, 1349m, 1235m, 1078w, 999w, 736s, 691s, 482s, 468w; ^{1}H NMR (400 MHz, $CDCl_3$, *cis*:*trans* = *ca*. 4:1) δ 7.75 (dd, *J* = 7.9, 1.7 Hz), 7.59–7.54 (m), 7.46–7.33 (m), 7.33–7.19 (m), 7.20–7.12 (m), 2.37–2.29 (m, 2H, *cis*), 1.63–1.56 (m, 2H, *cis*), 1.29 (s, 4H, *trans*); UV–Vis (CH_2Cl_2, nm) λ_{max} 288 (ε = 18040); MS (LIFDI$^+$) *m*/*z* 896.88 ([M]$^+$); Elemental anal.: C: 52.21, H: 3.76, N: 1.49, $C_{40}H_{34}As_2BrNO_2Pd{\cdot}0.24C_4H_4O_2NBr$ requires C: 52.45, H: 3.76, N: 1.83 (this ratio has been corroborated by ^{1}H NMR spectroscopy).

For X-ray crystallographic data (*trans*-isomer), see Appendix 3.

Lab book reference number: TOR-6-532

***cis*-Bromobis(tri(2-furyl)phosphine)(*N*-succinimide)palladium(II) (282)**

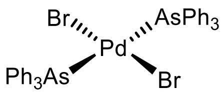


Prepared using general procedure A (L = $P(2\text{-}Fu)_3$), affording the *title compound* as a light brown powder (254 mg, 88%).

M.P. 90–93 °C (dec.); IR (ATR, cm^{-1}) ν_{max} 1712w, 1633m, 1455w, 1350w, 1235m, 1215m, 1125m, 1010s, 752s, 590m, 535s, 503s; ^{1}H NMR (400 MHz, CD_2Cl_2, *cis*:*trans* = *ca*. 9:1) δ 7.76–7.74 (m, 6H, *trans*), 7.65 (td, *J* = 1.9, 0.7 Hz, 3H, *cis*), 7.51 (td, *J* = 1.8, 0.7 Hz, 3H, *cis*), 7.30 (dd, *J* = 3.6, 1.0 Hz, 6H, *trans*), 7.12 (ddd, *J* = 3.5, 2.5, 0.7, 3H, *cis*), 7.03–6.99 (m, 3H, *cis*), 6.57 (ddd, *J* = 3.6, 1.9, 1.0 Hz, 6H, *trans*), 6.47 (dt, *J* = 3.4, 1.6 Hz, 3H, *cis*), 6.42 (dt, *J* = 3.4, 1.6 Hz, 3H, *cis*), 2.42–2.34 (m, 2H, *cis*), 2.17–2.09 (m, 2H, *cis*), 1.92 (s, 4H, *trans*); ^{31}P NMR (162 MHz, CD_2Cl_2) −25.7 (d, *J* = 13.5 Hz, *cis*), −26.6 (d, *J* = 13.5 Hz, *cis*), −32.0 (s, *trans*); UV–Vis (CH_2Cl_2, nm) λ_{max} 296 (ε = 14720); MS (LIFDI$^+$) *m*/*z* 748.91 ($[M]^+$); Elemental anal.: C: 44.56, H: 2.97, N: 1.70; $C_{28}H_{22}BrNO_8P_2Pd$ requires C: 44.91, H: 2.96, N: 1.87.

Lab book reference number: TOR-9-797

***trans*-Bistriphenylarsinepalladium(II) dibromide (283)**[235]



To a Schlenk tube containing $Pd(OAc)_2$ (100 mg, 0.45 mmol) and $AsPh_3$ (409 mg, 1.34 mmol) under N_2 was added dry CH_2Cl_2 (3 mL), and the resulting mixture was stirred for 15 min at RT, resulting in a green suspension. After this time, a solution of *N*-bromosuccinimide (recrystallized from H_2O and dried *in vacuo*, 80 mg, 0.45 mmol) in dry CH_2Cl_2 (3 mL) was added in one portion and the reaction mixture stirred for a further 15 min. An additional portion of dry CH_2Cl_2 (2 mL) was added, and the reaction stirred for another 15 min. The resulting orange suspension was filtered and dried in vacuo, affording the *title compound* as a yellow-orange solid (113 mg, 57% w.r.t NBS). Single crystals were grown by slow evaporation from $CHCl_3$.

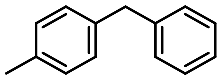
M.P. 212–216 °C (dec.); IR (ATR, cm^{-1}) ν_{max} 1581w, 1483m, 1436m, 1305w, 1188w, 1079m, 1024w, 999m, 737s, 691s, 476s, 464s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.65 (m, 12H), 7.47–7.35 (m, 18H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 134.7, 132.7, 130.3, 128.6;

MS (ESI^+) m/z (rel. %) 901 ($[M+Na]^+$, 100); HRMS (ESI^+) 900.8066 $[M+Na]^+$, $C_{36}H_{30}As_2Br_2NaPd$ requires 900.8053; Elemental anal.: C: 49.29, H: 3.30, N: 0, $C_{36}H_{30}As_2Br_2Pd$ requires C: 49.21, H: 3.44, N: 0.

For X-ray crystallographic data, see Appendix 3.

Lab book reference number: TOR-10-885

1-Benzyl-4-methylbenzene (286)[286]

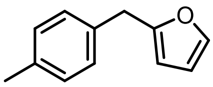


Title compound was synthesised using general procedure C, isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w/w*, petrol) as a colourless oil (18.8 mg, 88%).

R_f 0.56 (ether/petrol, 1:99, *v/v*); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 7.22–7.17 (m, 3H), 7.10 (s, 4H), 3.95 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 138.2, 135.7, 129.3, 129.0, 129.0, 128.6, 126.1, 41.7, 21.2; MS (EI^+) m/z (rel. %) 182 ($[M]^+$, 75), 167 ($[M-Me]^+$, 100).

Lab book reference number: TOR-9-760

2-[(4-Methylphenyl)methyl]furan (288)[287]

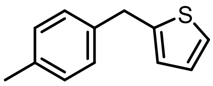


Title compound was synthesised using general procedure C, isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w/w*, petrol) as a colourless oil (16.7 mg, 83%).

R_f 0.70 (ether/petrol, 1:9, *v/v*); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (m, 1H), 7.13 (s, 4H), 6.33–6.26 (m, 1H), 6.00 (d, J = 2.6 Hz, 1H), 3.94 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 141.6, 136.1, 135.2, 129.3, 128.7, 110.3, 106.2, 34.2, 21.2; MS (EI^+) m/z (rel. %) 172 ($[M]^+$, 100), 157 ($[M-Me]^+$, 75); HRMS (EI^+) 172.0888 $[M]^+$, $C_{12}H_{12}O$ requires 172.0888.

Lab book reference number: TOR-9-829

2-[(4-Methylphenyl)methyl]thiophene (290)[287]

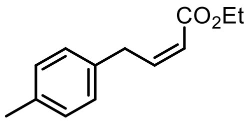


Title compound was synthesised using general procedure C, isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, petrol) as a colourless oil (21.3 mg, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18–7.10 (m, 5H), 6.98–6.87 (m, 1H), 6.80 (d, J = 2.6 Hz, 1H), 4.12 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.6, 137.5, 136.1, 129.4, 128.6, 126.9, 125.1, 124.0, 35.8, 21.2; MS (EI$^+$) *m*/*z* (rel. %) 188 ([M]$^+$, 100), 187 ([M−H]$^+$, 50), 173 ([M−Me]$^+$, 75); HRMS (EI$^+$) 188.0655 [M]$^+$, $C_{12}H_{12}S$ requires 188.0660.

Lab book reference number: TOR-10-848

Ethyl (2*Z*)-4-(4-methylphenyl)but-2-enoate (293)

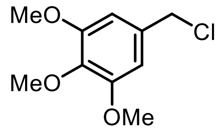


Title compound was synthesised using general procedure C, isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, ether/petrol, 5:95, *v*/*v*) as a colourless oil (19.9 mg, 83%).

R_f 0.26 (ether/petrol, 1:19, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2981m, 1717s, 1643m, 1514m, 1410m, 1387w, 1298w, 1192s, 1162s, 1096w, 1040m, 925w, 807m, 504w, 476w; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (s, 4H), 6.33 (dt, J = 11.4, 7.6 Hz, 1H), 5.83 (dt, J = 11.4, 1.7 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.98 (dd, J = 7.6, 1.7 Hz, 2H), 2.32 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 148.4, 136.6, 136.0, 129.4, 128.6, 119.9, 60.1, 34.9, 21.2, 14.4; MS (ESI$^+$) *m*/*z* (rel. %) 227 ([M+Na]$^+$, 100), 205 ([M+Na]$^+$, 15); HRMS (ESI$^+$) 227.1034 [M+Na]$^+$, $C_{13}H_{16}NaO_2$ requires 227.1043.

Lab book reference number: TOR-10-846

3,4,5-Trimethoxybenzylchloride (295)[245]

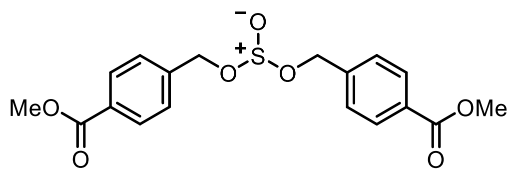


Thionyl chloride (403 μL, 5.55 mmol) was added dropwise to a solution of 3,4,5-trimethoxybenzyl alcohol (1.0 g, 5.05 mmol) in toluene (5 mL) at 0 °C. The resulting solution was stirred for 40 min at RT, before the volatiles were removed *in vacuo* to afford the *title compound* as an off-white solid (1.09 g, 99%).

M.P. 57–59 °C (lit.[288] 58–60 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (s, 2H), 4.54 (s, 2H), 3.87 (s, 6H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 138.2, 133.1, 105.8, 61.0, 56.3, 47.0; MS (ESI$^+$) *m/z* (rel. %) 239 ([M+Na]$^+$, 100), 217 ([M+H]$^+$, 10), 181 ([M−Cl]$^+$, 100); HRMS (ESI$^+$) 239.0445 [M+Na]$^+$, $C_{10}H_{13}NaClO_3$ requires 239.0445.

Lab book reference number: TOR-9-789

Methyl 4-[([4-(methoxycarbonyl)phenyl]methoxysulfinyl)oxymethyl]benzoate (297)

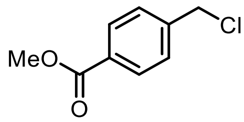


Thionyl chloride (156 μL, 2.15 mmol) was added dropwise to a solution of methyl 4-(hydroxymethyl)benzoate (325 mg, 1.96 mmol) in toluene (2 mL) at 0 °C. The resulting solution was stirred for 2 h at RT, before the volatiles were removed *in vacuo* to afford the *title compound* as a white solid (323 mg, 87%).

M.P. 95–97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 8.1 Hz, 4H), 7.38 (d, J = 8.1 Hz, 4H), 5.07 (d, J = 12.4 Hz, 2H), 4.98 (d, J = 12.4 Hz, 2H), 3.92 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 140.0, 130.5, 130.1, 128.1, 63.5, 52.4; MS (ESI$^+$) *m/z* (rel. %) 401 ([M+Na]$^+$, 100), 380 ([M+H]$^+$, 20); HRMS (ESI$^+$) 401.0647 [M+Na]$^+$, $C_{18}H_{18}NaO_7S$ requires 401.0665.

Lab book reference number: TOR-9-827

Methyl 4-(chloromethyl)benzoate (299)[247]

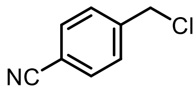


Methanol (950 μL, 21.6 mmol) was added dropwise to a solution of 4-(chloromethyl)benzoyl chloride (815 mg, 4.31 mmol) and triethylamine (903 μL, 6.47 mmol) in $CHCl_3$ (60 mL) at 0 °C. The resulting solution was stirred at RT for 15 h before being quenched with water (60 mL). The layers were separated, and the organic layer was dried over $MgSO_4$, filtered and evaporated to afford the *title compound* as a white solid (828 mg, >99%).

M.P. 35–36 °C (lit.[246] 37–38 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H), 4.61 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 142.4, 130.3, 130.2, 128.6, 52.4, 45.5; MS (ESI$^+$) *m/z* (rel. %) 207 ([M+Na]$^+$, 100), 184 ([M+H]$^+$, 10), 149 ([M−Cl]$^+$, 60); HRMS (ESI$^+$) 207.0176 [M+Na]$^+$, $C_9H_9NaClO_2$ requires 207.0183.

Lab book reference number: TOR-9-838

4-Cyanobenzylchloride (302)[248]

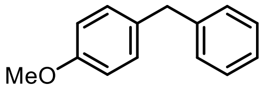


Sodium borohydride (324 mg, 8.39 mmol) was added to a stirred solution of 4-cyanobenzaldehyde (1.0 g, 7.63 mmol) in MeOH (30 mL). After stirring for 30 min, the reaction mixture was concentrated *in vacuo* and the residue dissolved in CH_2Cl_2 (30 mL), washed with water (3 × 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was then dissolved in toluene (5 mL) and cooled to 0 °C. Thionyl chloride (2.5 mL, 33.7 mmol) was added dropwise and the resulting solution stirred for 30 min at RT. After this time, the volatiles were removed *in vacuo* to afford the *title compound* as an off-white solid (701 mg, 61%).

M.P. 78–79 °C (lit.[289] 77–78 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 4.60 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5, 132.7, 129.3, 118.6, 112.4, 45.1; MS (EI$^+$) *m/z* (rel. %) 151 ([M]$^+$, 30), 116 ([M−Cl]$^+$, 100); HRMS (EI$^+$) 151.0188 [M]$^+$, C_8H_6NCl requires 151.0189.

Lab book reference number: TOR-10-871, TOR-10-872

1-Benzyl-4-methoxybenzene (304)[286]

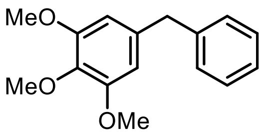


Title compound was synthesised using general procedure C, isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, ether/petrol, 1:99, *v*/*v*) as a colourless oil (21.3 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.26 (m, 2H), 7.23–7.15 (m, 3H), 7.13–7.09 (m, 2H), 6.86–6.81 (m, 2H), 3.93 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 141.7, 133.4, 130.0, 129.0, 128.6, 126.1, 114.0, 55.4, 41.2; MS (EI$^+$) *m*/*z* (rel. %) 198 ([M]$^+$, 100), 197 ([M−H]$^+$, 45), 167 ([M−OMe]$^+$, 40), 121 ([M−Ph]$^+$, 25); HRMS (EI$^+$) 198.1053 [M]$^+$, $C_{14}H_{14}O$ requires 198.1045.

Lab book reference number: TOR-9-765

5-Benzyl-1,2,3-trimethoxybenzene (305)

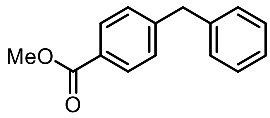


Title compound was synthesised using general procedure C, isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, ether/petrol, 2:98, *v*/*v*) as a colourless oil (25.1 mg, 83%).

R_f 0.24 (ether/petrol, 3:7, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2936m, 2837w, 1589m, 1505m, 1495m, 1452m, 1420m, 1329m, 1236s, 1183w, 1124s, 1009m, 970w, 844w, 782w, 702m, 593w;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 2H), 7.27–7.16 (m, 3H), 6.40 (s, 2H), 3.93 (s, 2H), 3.82 (s, 3H), 3.81 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 141.0, 136.9, 128.9, 128.6, 126.3, 106.1, 61.0, 56.2, 42.4; MS (ESI$^+$) *m*/*z* (rel. %) 281 ([M+Na]$^+$, 100), 259 ([M+H]$^+$, 60); HRMS (ESI$^+$) 259.1320 [M+H]$^+$, $C_{16}H_{19}O_3$ requires 259.1329.

Lab book reference number: TOR-9-790

Methyl 4-benzylbenzoate (306)[286]

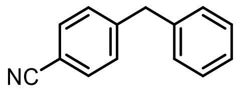


Title compound was synthesised using general procedure C, isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, ether/petrol, 3:97→5:95, *v*/*v*) as a colourless oil (17.8 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.3 Hz, 2H), 7.33–7.20 (m, 3H), 7.22–7.13 (m, 2H), 4.03 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 146.7, 140.3, 130.0, 129.1, 128.7, 128.2, 126.5, 52.2, 42.1; MS (ESI$^+$) *m*/*z* (rel. %) 249 ([M+Na]$^+$, 100), 227 ([M+Na]$^+$, 15); HRMS (ESI$^+$) 249.0882 [M+Na]$^+$, $C_{15}H_{14}NaO_2$ requires 249.0886.

Lab book reference number: TOR-9-844

4-Benzylbenzonitrile (307)[290]

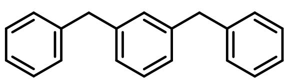


Title compound was synthesised using general procedure C (with a reaction temperature of 40 °C), isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, ether/petrol, 2:98→5:95, *v*/*v*) as a colourless oil (21.3 mg, 94%).

R_f: 0.36 (ether/petrol, 1:9, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3029w, 2922w, 2227s, 1603m, 1495m, 1454m, 1414m, 1261w, 1177w, 1074w, 1021m, 915w, 855m, 797s, 761s, 725s, 698s, 593s, 543s, 494m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.52 (m, 2H), 7.36–7.19 (m, 5H), 7.18–7.09 (m, 2H), 4.03 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 139.5, 132.5, 129.8, 129.1, 128.9, 126.8, 119.1, 110.2, 42.1; MS (APCI$^+$) *m*/*z* (rel. %) 206 ([M+H]$^+$, 100); HRMS (APCI$^+$) 194.0957 [M+H]$^+$, $C_{14}H_{12}N$ requires 194.0964.

Lab book reference number: TOR-10-880

1,3-Dibenzylbenzene (309)[291]

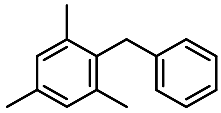


Title compound was synthesised using general procedure C, isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, petrol) as a colourless oil (24.0 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.26 (m, 4H), 7.23–7.16 (m, 7H), 7.06 (t, J = 1.8 Hz, 1H), 7.02 (dd, J = 7.6, 1.8 Hz, 2H), 3.95 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4, 141.3, 129.8, 129.1, 128.7, 128.6, 126.9, 126.2, 42.0; MS (EI$^+$) m/z (rel. %) 258 ([M]$^+$, 75), 167 ([M−CH_2Ph]$^+$, 100); HRMS (EI$^+$) 258.1416 [M]$^+$, $C_{20}H_{18}$ requires 258.1409.

Lab book reference number: TOR-9-773

2-Benzyl-1,3,5-trimethylbenzene (311)[292]

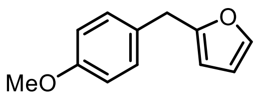


Title compound was synthesised using general procedure C, isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, petrol) and preparatory thin layer chromatography (SiO_2, *n*-pentane) as a colourless oil (17.8 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.17 (m, 2H), 7.20–7.10 (m, 1H), 7.06–6.97 (m, 2H), 6.89 (s, 2H), 4.02 (s, 2H), 2.30 (s, 3H), 2.21 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.2, 137.2, 135.8, 133.9, 129.0, 128.5, 128.0, 125.8, 34.8, 21.1, 20.3; MS (EI$^+$) m/z (rel. %) 210 ([M]$^+$, 75), 195 ([M−Me]$^+$, 100), 180 ([M−2Me]$^+$, 25), 165 ([M−3Me]$^+$, 20); HRMS (EI$^+$) 210.1413 [M]$^+$, $C_{16}H_{18}$ requires 210.1409.

Lab book reference number: TOR-9-782

2-[(4-Methoxyphenyl)methyl]furan (312)[293]

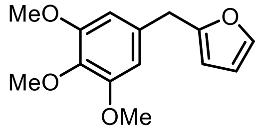


Title compound was synthesised using general procedure C, isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, ether/petrol, 1:99, *v*/*v*) as a colourless oil (19.6 mg, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, J = 1.9, 0.9 Hz, 1H), 7.16 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.29 (dd, J = 3.2, 1.9 Hz, 1H), 5.98 (dd, J = 3.2, 0.9 Hz, 1H), 3.92 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 155.2, 141.5, 130.3, 129.8, 114.1, 110.3, 106.1, 55.4, 33.8; MS (EI$^+$) m/z (rel. %) 188 ([M]$^+$, 100), 173 ([M−Me]$^+$, 10), 157 ([M−MeO]$^+$, 20); HRMS (EI$^+$) 188.0840 [M]$^+$, $C_{12}H_{12}O_2$ requires 188.0837.

Lab book reference number: TOR-9-821

2-[(3,4,5-Trimethoxyphenyl)methyl]furan (313)

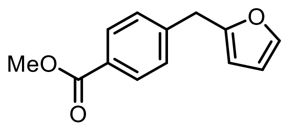


Title compound was synthesised using general procedure C, isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, ether/petrol, 1:9, *v*/*v*) as a colourless oil (22.3 mg, 77%).

R_f: 0.22 (ether/petrol, 3:7, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2938w, 2838w, 1590m, 1505m, 1457m, 1421m, 1334m, 1236s, 1183w, 1122s, 1008s, 970w, 806w, 729m, 650w, 660w, 528w; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, J = 1.9, 0.9 Hz, 1H), 6.45 (s, 2H), 6.31 (dd, J = 3.2, 1.9 Hz, 1H), 6.05 (dd, J = 3.2, 0.9 Hz, 1H), 3.91 (s, 2H), 3.83 (s, 6H), 3.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 153.4, 141.7, 136.7, 133.9, 110.4, 106.5, 105.8, 61.0, 56.2, 34.9; MS (ESI$^+$) *m*/*z* (rel. %) 271 ([M+Na]$^+$, 100), 249 ([M+H]$^+$, 55); HRMS (ESI$^+$) 271.0948 [M+Na]$^+$, $C_{14}H_{16}NaO_4$ requires 271.0941.

Lab book reference number: TOR-9-830

Methyl 4-(furan-2-ylmethyl)benzoate (314)

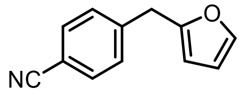


Title compound was synthesised using general procedure C, isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, ether/petrol, 3:97→5:95, *v*/*v*) as a colourless oil (18.8 mg, 74%).

R_f 0.16 (ether/petrol, 1:19, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2952w, 1718s, 1612m, 1506w, 1435m, 1417m, 1277s, 1178m, 1150w, 1105s, 1020m, 1011m, 939w, 794w, 727s, 600m, 491w; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 8.2 Hz, 2H), 7.35–7.32 (m, 1H), 7.30 (d, J = 8.2 Hz, 2H), 6.31–6.29 (m, 1H), 6.03 (d, J = 2.7 Hz, 1H), 4.02 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 153.6, 143.6, 141.9, 130.0, 128.8, 128.6, 110.5, 106.8, 52.2, 34.6; MS (ESI$^+$) *m*/*z* (rel. %) 239 ([M+Na]$^+$, 100), 217 ([M+Na]$^+$, 30); HRMS (ESI$^+$) 239.0678 [M+Na]$^+$, $C_{13}H_{12}NaO_3$ requires 239.0679.

Lab book reference number: TOR-10-845

4-(Furan-2-ylmethyl)benzonitrile (315)

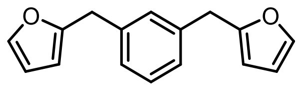


Title compound was synthesised using general procedure C (with a reaction temperature of 40 °C), isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, ether/petrol, 2:98→4:96, *v*/*v*) as a colourless oil (18.6 mg, 87%).

R_f: 0.38 (ether/petrol, 1:9, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2922w, 2229s, 1980w, 1715m, 1608s, 1505s, 1417m, 1150m, 1011s, 939m, 852m, 811s, 736s, 599m, 550s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.57 (m, 2H), 7.34–7.30 (m, 3H), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.06 (dq, *J* = 3.2, 0.9 Hz, 1H), 4.03 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 143.9, 142.2, 132.5, 129.6, 119.0, 110.6, 110.5, 107.2, 34.6; MS (ESI^+) *m*/*z* (rel. %) 206 ($[M+Na]^+$, 100); HRMS (ESI^+) 206.0583 $[M+Na]^+$, $C_{12}H_9NNaO$ requires 206.0576.

Lab book reference number: TOR-10-878

1,3-Di(furan-2-ylmethyl)benzene (316)

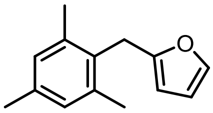


Title compound was synthesised using general procedure C, isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, ether/petrol, 1:99→2:98, *v*/*v*) as a colourless oil (24.8 mg, 89%).

R_f 0.15 (petrol); IR (thin film, cm^{-1}) ν_{max} 2908w, 1592m, 1506m, 1446m, 1250w, 1449m, 1073m, 1009s, 939m, 884m, 798m, 719s, 599s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 1.9, 0.9 Hz, 2H), 7.25–7.21 (m, 1H), 7.12–7.07 (m, 3H), 6.29 (dd, *J* = 3.2, 1.9 Hz, 2H), 5.99 (dd, *J* = 3.2, 0.9 Hz, 2H), 3.95 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.6, 141.6, 138.5, 129.3, 128.8, 127.0, 110.4, 106.4, 34.5; MS (EI^+) *m*/*z* (rel. %) 238 ($[M]^+$, 100), 157 ($[M-CH_2Fu]^+$, 80); HRMS (EI^+) 238.0994 $[M]^+$, $C_{16}H_{14}O_2$ requires 238.0994.

Lab book reference number: TOR-9-824

2-[(2,4,6-Trimethylphenyl)methyl]furan (317)

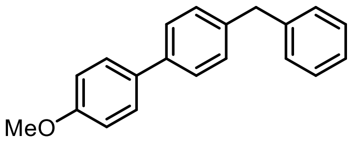


Title compound was synthesised using general procedure C, isolated after flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, petrol) as a colourless oil (19.5 mg, 83%).

R_f 0.31 (petrol); IR (thin film, cm^{-1}) ν_{max} 2920m, 1614m, 1593m, 1506m, 1485m, 1446m, 1377w, 1168m, 1135w, 1074m, 1007s, 934w, 885w, 852m, 789m, 727s, 679w, 599m, 557w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.28 (m, 1H), 6.87 (s, 2H), 6.23 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.76 (dd, *J* = 3.2, 1.1 Hz, 1H), 3.94 (s, 2H), 2.30 (s, 6H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2, 141.2, 137.0, 136.1, 131.6, 129.0, 110.2, 105.5, 28.4, 21.0, 20.0; MS (EI$^+$) *m*/*z* (rel. %) 200 ([M]$^+$, 100), 185 ([M−Me]$^+$, 75), 144 (50), 132 ([M−Fu−H]$^+$, 85); HRMS (EI$^+$) 200.1202 [M]$^+$, $C_{14}H_{16}O$ requires 200.1201.

Lab book reference number: TOR-9-840

1-Benzyl-4-(4-methoxyphenyl)benzene (320)[294]



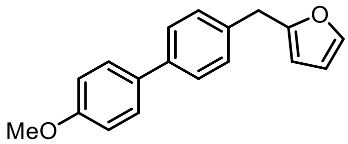
Reaction between 4-bromobenzyl chloride (1 eq.) and tributylphenylstannane (1.1 eq.) was conducted according to general procedure C. At the end of the reaction time (24 h), 4-methoxybenzeneboronic acid (26.7 mg, 0.176 mmol) was added, followed by 2 M aq. Na_2CO_3 (1 mL) and the reaction heated to 60 °C for 20 h with vigorous stirring. After this time the work-up was conducted according to general procedure 2 and purification by flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, ether/petrol, 1:199, *v*/*v*) and preparatory thin layer chromatography (SiO_2, ether/petrol, 1:9, *v*/*v*) afforded the *title compound* as a white solid (23.3 mg, 73%).

M.P. 93–95 °C (lit.[294] 100–101 °C); R_f 0.24 (ether/petrol, 1:19, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 3027w, 2912w, 2838w, 1606m, 1582w, 1528w, 1498s, 1454m, 1402w, 1279m, 1250s, 1211m, 1179m, 1074w, 1037s, 1015m, 907s, 828s, 793s, 730s, 698s, 668m, 598m, 554w, 544w, 498m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.9 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.33–7.27 (m, 2H), 7.26–7.20 (m, 5H), 6.96 (d, *J* = 8.9 Hz, 2H), 4.01 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 141.2, 139.7, 138.8, 133.7, 129.4, 129.1, 128.6, 128.1, 126.9, 126.3, 114.3, 55.5, 41.7; MS (EI$^+$) *m*/*z* (rel. %) 274 ([M]$^+$, 100), 259

([M−Me]$^+$, 15), 243 ([M−OMe]$^+$, 10), 197 ([M−Ph]$^+$, 10); HRMS (EI$^+$) 274.1348 [M]$^+$, $C_{20}H_{18}O$ requires 274.1358.

Lab book reference number: TOR-10-857

2-([4-(4-Methoxyphenyl)phenyl]methyl)furan (321)



Reaction between 4-bromobenzyl chloride (1 eq.) and 2-(tributylstannyl)furan (1.1 eq.) was conducted according to general procedure C. At the end of the reaction time (3 h), 4-methoxybenzeneboronic acid (26.7 mg, 0.176 mmol) was added, followed by 2 M aq. Na_2CO_3 (1 mL) and the reaction heated to 60 °C for 19 h with vigorous stirring. After this time the work-up was conducted according to general procedure 2 and purification by flash chromatography (SiO_2–K_2CO_3, 9:1, *w*/*w*, ether/petrol, 1:99→2:98, *v*/*v*) afforded the *title compound* as a white solid (22.5 mg, 73%).

M.P. 93–94 °C; R_f 0.25 (ether/petrol, 1:19, *v*/*v*); IR (thin film, cm^{-1}) ν_{max} 2962w, 2837w, 1607m, 1500s, 1291m, 1274m, 1254s, 1182m, 1150w, 1037s, 1011s, 937w, 908w, 816s, 759s, 733s, 601w, 505w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.9 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 7.35 (dd, J = 1.9, 0.8 Hz, 1H), 7.28 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 6.31 (dd, J = 3.0, 1.9 Hz, 1H), 6.05 (dd, J = 3.0, 0.8 Hz, 1H), 4.00 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 154.7, 141.7, 139.2, 136.7, 133.6, 129.2, 128.2, 127.0, 114.3, 110.4, 106.4, 55.5, 34.2; MS (EI$^+$) *m*/*z* (rel. %) 264 ([M]$^+$, 100), 249 ([M−Me]$^+$, 10); HRMS (EI$^+$) 264.1147 [M]$^+$, $C_{18}H_{16}O_2$ requires 264.1150.

Lab book reference number: TOR-10-853

Appendix 1: Published papers

The following section contains, in chronological order, reproductions of papers which have been published with the contributions of the author in connection with the work described in this thesis.

1. Burns, M. J.; Ronson, T. O.; Taylor, R. J. K.; Fairlamb, I. J. S.; 4-Hydroxy-6-alkyl-2-pyrones as nucleophilic coupling partners in Mitsunobu reactions and oxa-Michael additions, *Beilstein J. Org. Chem.*, **2014**, *10*, 1159–1165.

2. Ronson, T. O.; Taylor, R. J. K.; Fairlamb, I. J. S.; Palladium-catalysed macrocyclisations in the total synthesis of natural products, *Tetrahedron*, **2015**, *71*, 989–1009.

3. Ronson, T. O.; Carney, J. R.; Taylor, R. J. K.; Fairlamb, I. J. S.; AsCat and FurCat: New Pd catalysts for selective room-temperature Stille cross-couplings of benzyl chlorides with organostannanes, *Chem. Commun*., **2015**, *51*, 3466–3469.

4. Ronson, T. O.; Voelkel, M. H. H.; Taylor, R. J. K.; Fairlamb, I. J. S.; Macrocyclic polyenynes: A stereoselective route to vinyl-ether-containing skipped diene systems, *Chem. Commun*., **2015**, *51*, 8034–8036.

Beilstein Journal of Organic Chemistry

4-Hydroxy-6-alkyl-2-pyrones as nucleophilic coupling partners in Mitsunobu reactions and oxa-Michael additions

Michael J. Burns, Thomas O. Ronson, Richard J. K. Taylor and Ian J. S. Fairlamb*

Full Research Paper

Open Access

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* Corresponding author

Keywords:
heterocycles; Mitsunobu reaction; oxa-Michael addition; 2-pyrone; vinyl ethers

Beilstein J. Org. Chem. **2014,** *10,* 1159–1165.
doi:10.3762/bjoc.10.116

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Accepted: 15 April 2014
Published: 20 May 2014

Associate Editor: B. Stoltz

Abstract

Two mild and efficient strategies have been developed for the *O*-functionalisation of 4-hydroxy-6-alkyl-2-pyrones, by using them as nucleophilic partners in oxa-Michael additions and the Mitsunobu reaction. The reactions proceed in moderate to excellent yields on a range of substrates containing useful functionality. The reactions serve as practical and valuable synthetic methods to construct complex 2-pyronyl ethers, which are found embedded in a number of natural products.

Introduction

The 2-pyrone motif is a prevalent structural feature of many complex natural products and biologically active compounds [1,2]. Various functionalised 2-pyrones have been identified as promising candidates for the treatment of illnesses ranging from Alzheimer's disease [3] to cancer [4]. An important sub-class of pyrones are the 4-hydroxy-2-pyrones, which are sometimes found embedded into larger natural products as pyronyl ethers, such as in the phacelocarpus 2-pyrones **1** and **2** (Figure 1). These compounds are secondary metabolites isolated from the Australian marine red alga *Phacelocarpus labillardieri* [5]; similar compounds from the same family have been shown to exhibit phospholipase A_2 (PLA_2) inhibitory activity [6]. Whilst the chemistry of 2-pyrones is generally well-developed [7], efficient routes to these types of complex structural units are elusive, and the total synthesis of these and similar natural products remains a challenge [8].

Simple 2-pyrones such as 4-hydroxy-6-methyl-2-pyrone (triacetic acid lactone, **3a**, Figure 1) are readily and cheaply available, making them seemingly ideal building blocks for the

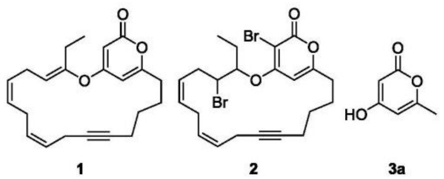
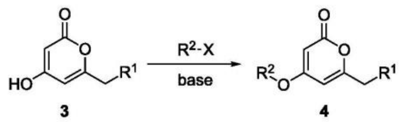


Figure 1: The phacelocarpus 2-pyrones **1** and **2**.

synthesis of such complex pyrone-containing molecules. As heterocyclic aromatic enols, they have a high acidity and dense functionality which leads to a diverse reactivity profile. This means that 4-hydroxy-2-pyrones are also useful precursors to a number of other structural units and versatile intermediates in organic synthesis.

Despite, or perhaps because of, this varied reactivity, *O*-functionalisation reactions of 4-hydroxy-2-pyrones, to afford 2-pyronyl ethers (e.g., Scheme 1), remain almost entirely limited to reactions with methylating agents or simple alkyl or acyl halides. These often require heating with a base such as K_2CO_3 or DBU, and the available functionality is therefore limited to esters or simple primary alkyl groups [9-11]. Even in simple cases the yields obtained are variable as the 2-pyrone unit is prone to degradation under harsh conditions, representing an interesting synthetic chemistry challenge to address. The ability to install more complex functionality on the hydroxy group of 6-alkyl-4-hydroxy-2-pyrones would be of considerable synthetic value.



Scheme 1: Generalised *O*-functionalisation of 6-alkyl-4-hydroxy-2-pyrones **3**.

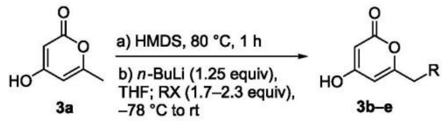
The Mitsunobu reaction is a well-established, widely used and invaluable tool for synthetic chemists [12]. It is usually employed to couple an acidic nucleophile with a primary or secondary alcohol, and as a mild reaction it tolerates a range of functionality in both coupling partners, allowing it to be used on complex and sensitive substrates. Given the high acidity of hydroxypyrones such as **3** (Scheme 1; R^1 = H, pK_a = 4.94 [13]), they would appear to be ideal coupling partners in the Mitsunobu reaction.

We recently published an example of the Mitsunobu reaction using the compound 4-hydroxy-6-methyl-2-pyrone (**3a**) [14]. To the best of our ability, we could find only limited precedent for this procedure being used previously in this way [15-17]. In our case, we were able to further modify the resulting pyronyl ether forming a trisubstituted enol ether, which then underwent a Suzuki–Miyaura cross-coupling or direct arylation-type reaction. As part of our extensive studies on reactions involving 2-pyrone derivatives, we report herein a significant expansion of the Mitsunobu protocol to a variety of different coupling partners, along with an alternative route to the formation of 2-pyronyl enol ethers using an oxa-Michael addition to propiolate esters. Both procedures are mild, tolerate a wide range of functionality, and afford good to excellent yields of products in the majority of cases.

Results and Discussion

Mitsunobu reactions

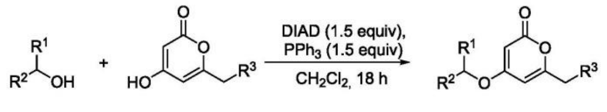
Using the standard conditions of stirring diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in dichloromethane at room temperature for 18 hours, we tested the substrate scope of the reaction (Table 1). In addition to the silyl-protected alcohol reported previously [14] (Table 1, entry 3), we found that a variety of useful functionality on the alcohol was well-tolerated, including a terminal alkene (Table 1, entry 2), a tosylate leaving group (Table 1, entry 4), and a halide (Table 1, entry 5). Somewhat more exotic functional groups such as a phosphonate ester (Table 1, entry 6) or a dimethyl acetal (Table 1, entry 7) were still tolerated in the reaction, albeit in more modest yields. A variety of alkylated 2-pyrones **3b–e** were synthesised according to the method of Hsung and co-workers [18], in order to further explore the scope of the Mitsunobu process. This involves a one-pot silyl-protection of the hydroxy group of 6-methyl-4-hydroxy-2-pyrone **3a** with HMDS, followed by lithiation and alkylation (Scheme 2).



Scheme 2: Synthesis of alkylated 2-pyrones **3b–e**.

These more structurally complex systems also underwent Mitsunobu reaction with various alcohols in good to excellent yields (Table 1, entries 8–12). Compounds **4i–l** could find further utility in the synthesis of phacelocarpus 2-pyrones in the future.

Table 1: Synthesis of 2-pyronyl ethers **4a–l**.



5 (1.5 equiv) + **3** (1 equiv) → **4**

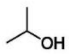
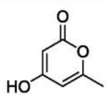
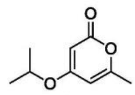
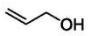
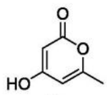
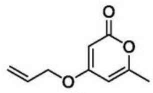
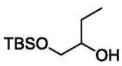
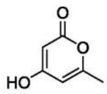
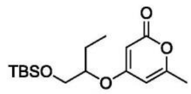
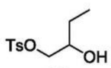
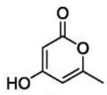
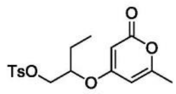
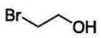
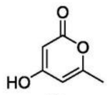
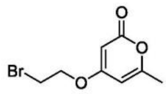
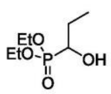
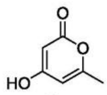
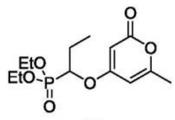
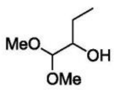
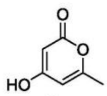
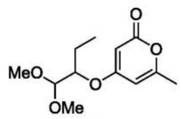
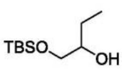
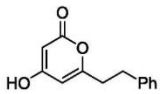
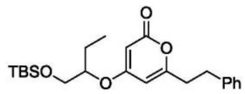
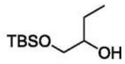
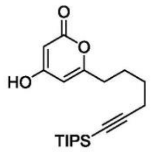
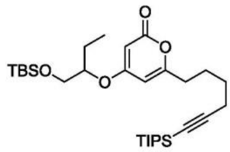
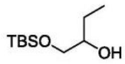
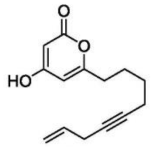
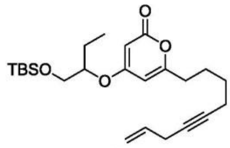
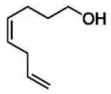
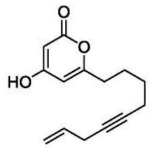
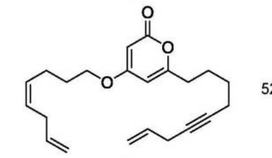
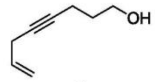
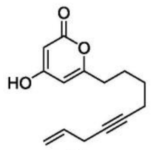
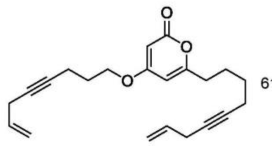
Entry	Alcohol	Pyrone	Product	Yield (%)[a]
1	 **5a**	 **3a**	 **4a**	70
2	 **5b**	 **3a**	 **4b**	54
3	 **5c**	 **3a**	 **4c**	98
4	 **5d**	 **3a**	 **4d**	99
5	 **5e**	 **3a**	 **4e**	82
6	 **5f**	 **3a**	 **4f**	30
7	 **5g**	 **3a**	 **4g**	23
8	 **5b**	 **3b**	 **4h**	81

Table 1: Synthesis of 2-pyronyl ethers **4a–l**. (continued)

9	 **5b**	 **3c**	 **4i**	75
10	 **5b**	 **3d**	 **4j**	50
11	 **5h**	 **3d**	 **4k**	52
12	 **5i**	 **3d**	 **4l**	61

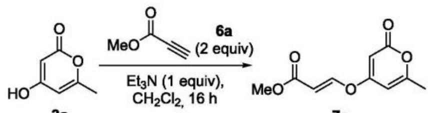
[a]Yield of product isolated following chromatography on silica gel.

Oxa-Michael additions

Whilst the formation of pyronyl ethers is useful in itself, the ability to introduce an unsaturated group onto the oxygen, leading to a pyronyl enol ether, would have additional value. This is a highly unusual motif found in some marine polyketide natural products (such as compound **1**, Figure 1). Conjugate addition to α,β-ynones represents an intuitive and efficient route to vinyl compounds, and is well-established with a plethora of oxygen-based nucleophiles [19]. Addition of highly acidic coupling partners can be challenging, however, due to the low nucleophilicity of the conjugate base in which the electron density is extensively delocalised. To the best of our ability we could not find a single previous published example of a Michael addition employing 4-hydroxy-2-pyrones.

Initial experiments reacting 4-hydroxy-2-pyrone **3a** with methyl propiolate (**6a**) in the presence of an amine base afforded only moderate yields of product **7a** (Table 2, entry 1). However,

Table 2: Michael addition reaction optimisation.



3a (1 equiv) **7a**

Entry	Temperature (°C)	Time (h)	Yield (%)[a]
1	20	2	48
2	20	16	63
3	45	16	82
4	80[b]	0.5	67

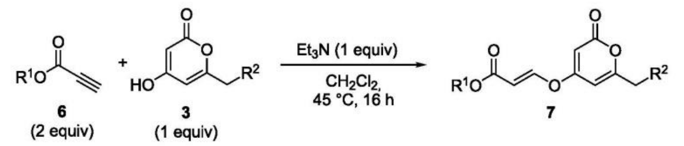
[a]Yield of product isolated following chromatography on silica gel.
[b]Reaction performed under microwave irradiation.

raising the temperature of the reaction and increasing the reaction time led to a significant increase in the conversion to product and an isolated yield of 82% (Table 2, entry 3). Further heating under pressure with microwave irradiation led to a decrease in yield.

Following reaction optimisation, we applied these conditions to a number of different propiolate esters and alkylated 4-hydroxy-2-pyrones (Table 3). Surprisingly, the tolerance of the reaction to different ester groups proved rather limited. The switch from methyl propiolate to *tert*-butyl propiolate (**6b**) led to a slight drop in yield (Table 3, entry 2), but moving to pentafluorophenyl propiolate (**6c**) reduced the yield to a modest 27% (Table 3, entry 3). An attempt with *N*-methoxy-*N*-methylpropiolamide (**6d**) led to no product formation (Table 3, entry 4), and significant recovery of starting material. Changes in the C-6 substituent on the pyrone were tolerated much better, with yields from good to excellent for a range of pyrones with methyl propiolate (Table 3, entries 5–8). A further attempt with pentafluorophenyl propiolate resulted in a poor yield (Table 3, entry 9).

As an extension to this methodology, we explored the addition of hydroxypyrones to both an allene and an internal alkyne to furnish a trisubstituted enol ether. Addition of 4-hydroxy-6-methyl-2-pyrone (**3a**) to the terminal allene **8** under the optimised conditions proceeded smoothly to give the *trans*-trisubstituted enol ether **9** in 52% yield (Scheme 3). However, numerous attempts to apply these conditions to an internal alkyne failed to furnish any desired product, presumably due to the steric influence of the additional methyl group. However, after an exhaustive screening of conditions (see Supporting Information File 1 for full details), we found that the addition of copper(I) iodide to the reaction mediated the addition of pyrone **3a** to ethyl 2-butynoate (**10**). The reaction was performed with a sub-stoichiometric quantity of DBU (whilst primarily functioning as a base, the DBU was also suspected to be acting partially as a co-solvent as the solubility of the **3a** was found to

Table 3: Synthesis of pyronyl vinyl ethers **7**.



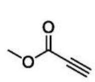
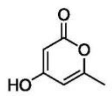
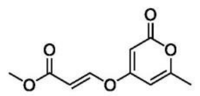
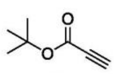
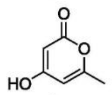
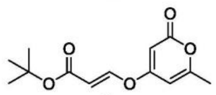
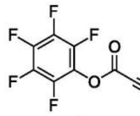
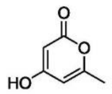
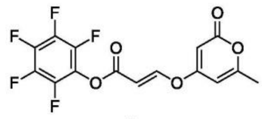
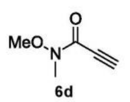
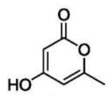
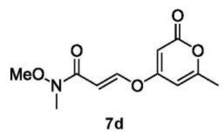
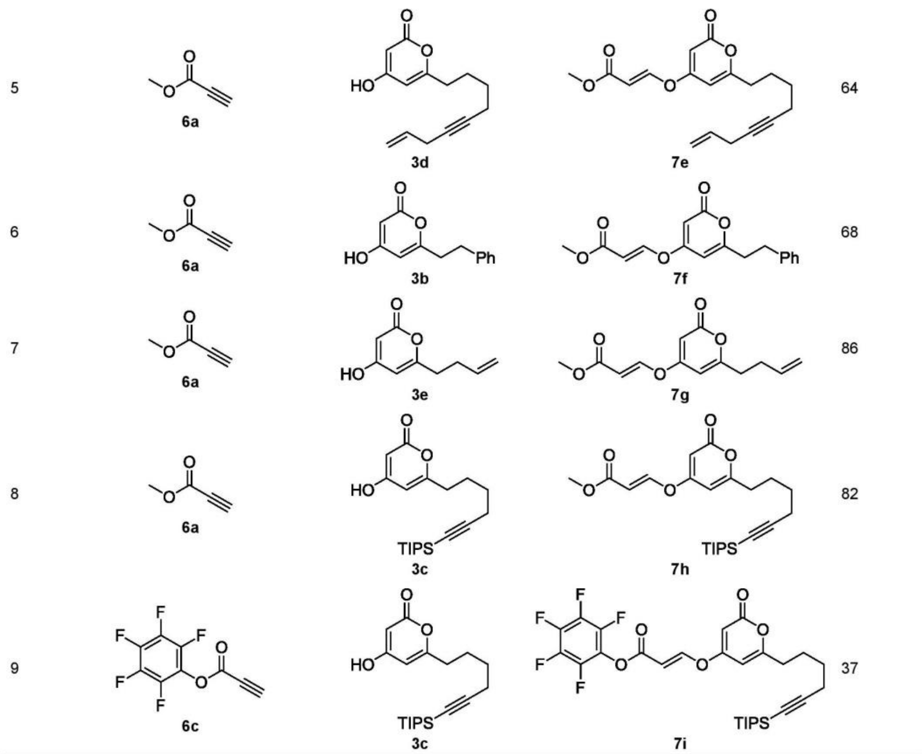
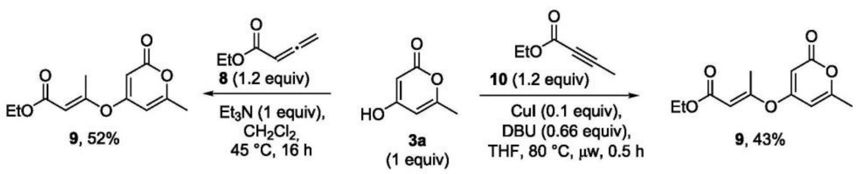
Entry	Electrophile	Pyrone	Product	Yield (%)[a]
1	 **6a**	 **3a**	 **7a**	82
2	 **6b**	 **3a**	 **7b**	61
3	 **6c**	 **3a**	 **7c**	27
4	 **6d**	 **3a**	 **7d**	0

Table 3: Synthesis of pyronyl vinyl ethers **7**. (continued)



[a]Yield of product isolated following chromatography on silica gel.



Scheme 3: Michael addition of **3a** to allene **8** and internal alkyne **10**.

be greatest at 0.66 equivalents) in THF under microwave irradiation (Scheme 3), and afforded the desired product in moderate yield after just 0.5 h (longer reaction times led to degradation of the product). Extension of the chain to an ethyl group (i.e., using ethyl 2-pentynoate) served to further reduce the reactivity towards addition and no product was formed even under the optimised conditions.

Conclusion

In conclusion, 4-hydroxy-6-alkyl-2-pyrones are effective coupling partners in Mitsunobu reactions and oxa-Michael additions. The reactions have been shown to tolerate a range of different functional groups by virtue of the mild conditions employed, affording the desired products in moderate to excellent yields in the majority of cases. This protocol offers a practical method for the synthesis of functionalized 2-pyronyl ethers which should find use in the synthesis of natural products and other bioactive compounds.

Experimental

General procedure 1: Mitsunobu reaction with 4-hydroxy-2-pyrones: To a stirred solution of the pyrone (1 equiv), triphenylphosphine (1.5 equiv) and alcohol (1.5 equiv), in dichloromethane (4 mL $mmol^{-1}$) under nitrogen either at 0 °C or ambient temperature, was carefully added DIAD (1.5 equiv) over 10–30 min (depending on scale), so as to avoid the generation of excess heat (<5 °C internal temperature increase). The solution was then stirred at rt (typically 18–25 °C) for 16 hours, and the solvent removed in vacuo. Byproduct phosphine oxide was removed from the crude residue by dissolving the product in ether (2 mL $mmol^{-1}$), and vacuum filtration to remove the solid oxide. The ether was then removed in vacuo and the residue purified via flash column chromatography to afford the desired product.

General procedure 2: Oxa-Michael addition with 4-hydroxy-2-pyrones: The pyrone (1 equiv), triethylamine (1 equiv) and propiolate ester (2 equiv) were stirred in CH_2Cl_2 (2 mL $mmol^{-1}$) at 45 °C for 16 h. The solvent was then removed in vacuo and the product purified via flash column chromatography to afford the desired product.

Supporting Information

Supporting Information File 1

Detailed experimental procedures, characterisation data for compounds **3b–e, 4a–l**, **5d**, **7a–i** and **9** and ^{1}H NMR spectra for novel compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-116-S1.pdf]

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Palladium-catalysed macrocyclisations in the total synthesis of natural products

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Contents

1. Introduction

Macrocyclic compounds occupy a singular position in the fields of chemistry and biology.[1,2] Their unique chemical, physical and medicinal properties make them distinct from acyclic compounds or those containing smaller rings. Much of the recent interest in large-ring compounds has derived from their favourable biological characteristics: the conformational constraint inherent in any cyclic system coupled with the flexibility of a large ring makes it possible to bind selectively to biological targets with high potency. This, along with their other drug-like properties such as good lipophilicity, membrane penetration and solubility, means that macrocycles are often excellent candidates for pharmaceutical compounds.[3–6] Indeed, macrocyclic compounds are finding increasing clinical use, especially as antitumour compounds, immunosuppressants, antibiotics and antifungals.

The majority of macrocyclic drug molecules are currently derived from naturally occurring compounds, either natural products employed directly in the clinic (e.g., vancomycin), or closely related analogues (e.g., ixabepilone,[7] a synthetic analogue of epothilone B). The total synthesis of such natural products has historically played an important part in the discovery of new macrocyclic drugs. A number of recent reviews have been published describing families of related biologically active macrocyclic natural products and their chemical synthesis.[8–11] They remain intriguing and challenging targets for chemists, and it is perhaps this synthetic challenge which has hindered the exploration of macrocyclic drugs much

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beyond those found in nature. Efficient synthetic routes to macrocycles are therefore of utmost importance in the quest for new therapeutic molecules.

There are a number of common methods used for the synthesis of macrocyclic natural products. Since a large number of macrocycles contain an ester or amide linkage, macrolactonisation and macrolactamisation have traditionally played a major role.[12] Since its popularisation by Grubbs, ring-closing olefin (alkene) metathesis has likewise become a major route for the synthesis of large-ring compounds.[13] Many other methods have also been used including substitution reactions and radical cyclisation approaches.[14] Whilst many of these methods have been employed with great success, they are not always efficient and frequently place specific functional-group constraints on the resulting macrocycle. Pd-catalysed reactions represent a major class of macrocyclisation reaction in the context of natural product total synthesis, which have been well developed and utilised over the past several decades. This review is intended to provide an overview of the different Pd-catalysed macrocyclisation reactions used in the synthesis of naturally occurring compounds. The review highlights the potential of Pd-catalysed macrocyclisations as a complementary but alternative approach to other commonly employed macrocyclisation strategies.

2. Palladium-catalysed macrocyclisation

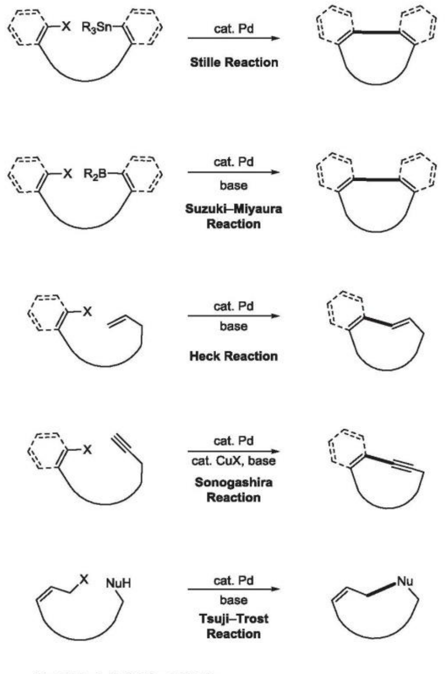
Pd catalysis has become an invaluable tool in the total synthesis of natural products, allowing the efficient and selective formation of carbon–carbon bonds.[15] The main reactions employed (Scheme 1) are the cross-coupling of a halide, or pseudohalide, with organostannanes (Stille),[16,17] organoboron compounds (Suzuki–Miyaura),[18,19] alkenes (Heck)[20,21] or terminal alkynes (Sonogashira).[22] The coupling of a nucleophile with an allylic electrophile such as an acetate or carbonate (Tsuji–Trost)[23,24] has also frequently been used. The sheer diversity of these different Pd-catalysed reactions makes them attractive methods for macrocycle formation, allowing a choice of disconnections and application to a huge variety of molecules with little constraint on functional groups. It is therefore no surprise that all of the above reactions have been used, to a greater or lesser extent, as macrocyclisation reactions in the total synthesis of natural products.

The kinetic and thermodynamic factors involved in macrocyclisation reactions have been the subject of detailed physical and theoretical studies, which are beyond the scope of this review.[25,26] However, in the cyclisation of any bifunctional compound, the main challenge to address is the competition between intramolecular reaction (cyclisation) and intermolecular reaction (di-, oligo- or polymerisation). High dilution techniques are thus often employed to favour the intramolecular reaction, despite the fact that they can lead to extended reaction times and necessitate the use of large volumes of solvent. These pitfalls can sometimes be circumvented by techniques such as slow addition of substrate or, in the case of metal-catalysed reactions, use of polymer-supported catalysts.[27]

In the following sections, examples are grouped according to the specific reaction which is employed in the macrocyclisation step of the total synthesis. The intention is to give the reader a broad, rather than exhaustive, overview of the many different ways in which Pd catalysis has been used in the construction of macrocyclic natural products, beginning with a brief historical outline and moving on to more recent examples. Where known, the catalyst loading and substrate concentration at which the reaction was conducted are given in each scheme.

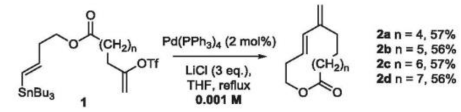
3. The Stille reaction

To date, the Stille cross-coupling reaction has unquestionably been the most widely utilised method of palladium-catalysed macrocyclisations in the field of natural product total synthesis. This can be partly explained by the fact that naturally occurring macrocycles frequently contain conjugated alkenes, a group which is arguably best accessed by the Stille reaction, but also due to its reliability, mildness, and the stability and ease of handling of the reagents required. All of these aspects lend the Stille reaction very well to the field of total synthesis.



Scheme 1. General scheme for Pd-catalysed macrocyclisation.

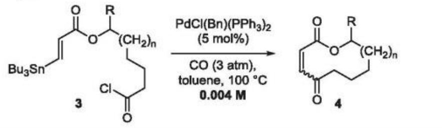
The first report of a Pd-catalysed macrocyclisation utilising an organostannane was published by Stille in 1987.[28] It was shown to be a viable methodology by employing relatively mild, high dilution conditions and achieving the efficient formation of a series of 12–15 membered rings (**2a–d**, Scheme 2). The authors noted that, remarkably, the yield of the transformation was apparently unaffected by the size of the ring under construction, with the 12-membered ring, a size, which had been previously observed to be particularly difficult to form, cyclising as easily as the rest. The authors later expanded on this initial study, demonstrating the effective use of polymer-supported palladium catalysts in carbonylative Stille macrocyclisations.[29]



Scheme 2. The first reported Stille macrocyclisation reaction (Stille and Tanaka, 1987).[28]

Another early study was performed by Baldwin and co-workers, examining the intramolecular cyclisation of acid chlorides with vinyl stannanes to form a range of ring sizes (Table 1).[30,31] They achieved the construction of a variety of rings (including a formal total synthesis of the antibiotic (±)-A26771B) in moderate to excellent yields, noting a much higher tendency towards dimerisation with smaller ring sizes (10 or 11 membered, indeed the 10-membered monomer was apparently not isolated).

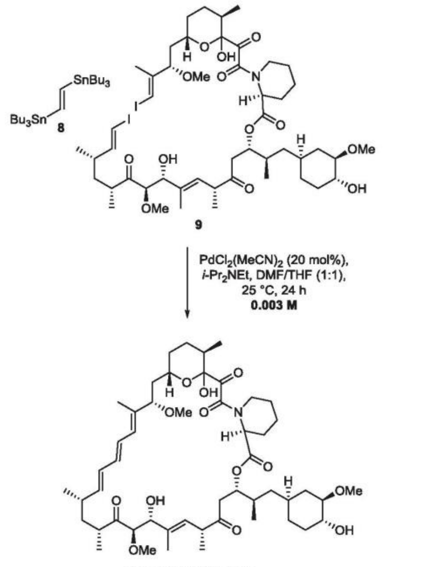
Table 1
Intramolecular carbonylative Stille coupling with a variety of ring sizes (Baldwin et al., 1991)[30]



Entry	R	n	Ring size	Product geometry	Yield (%)
1	H	11	20	*E*	48
2	H	7	16	*E*	53
3	Me	7	16	*E*	58
4	H	5	14	*E*	55
5	H	3	12	*Z*	41
6	H	2	11	*Z*	32 (+30 dimer)
7	H	1	10	—	0 (58 dimer only)

The authors also noted that reaction concentration is of great importance, with high concentrations (0.05–0.01 M) favouring intermolecular reactions and low concentrations (0.002 M) resulting mainly in side reactions such as protodestannylation.

It was not long before this methodology was being applied to complex natural product targets. In an early demonstration of the efficacy of this method, Hegedus and co-workers applied it to the total synthesis of the 14-membered macrolide (*S*)-zearalenone (**7**, Scheme 3).[32] During their studies they compared three different approaches: use of a vinyl stannane with either an aryl iodide or an aryl triflate, and the use of an aryl stannane with a vinyl triflate. The aryl iodide and vinyl stannane combination was found to be most effective, using $Pd(PPh_3)_4$ on a 20% cross-linked polystyrene support as catalyst, affording a yield of 54% for the macrocyclisation step.

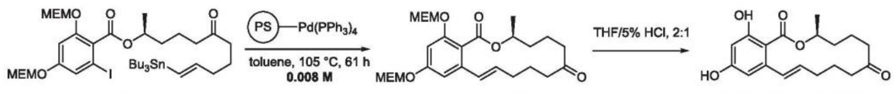


Rapamycin (**10**), 28%

Scheme 4. Stille 'stitching' cyclisation in the total synthesis of rapamycin (Nicolaou et al., 1993).[33]

compared to the commonly used PPh_3 ligand. Although they did not investigate any intramolecular examples, the potential benefits to macrocyclisation reactions are clear as the high dilution conditions used to avoid intermolecular reactions often lead to greatly reduced rates of reaction and concomitant side reactions.

The efficacy of this improved catalyst system was effectively demonstrated by Pattenden and Thom in their studies towards the total synthesis of the antitumour antibiotic leinamycin (**13**).[36]



5 **6**, 54% (*S*)-zearalenone (**7**), 80%

Scheme 3. Intramolecular Stille reaction using polystyrene-supported $Pd(PPh_3)_4$ in the total synthesis of (*S*)-zearalenone (Hegedus et al., 1991)[32] (MEM=β-methoxyethoxymethyl ether, PS=polystyrene).

An elegant demonstration of the potential of this method was reported by Nicolaou and co-workers in 1993.[33] In the final step of their total synthesis of rapamycin (**10**), a potent antibiotic and immunosuppressant isolated from *Streptomyces hygroscopius*, they reacted the acyclic diiodo precursor **9** with the distannane **8** to effect a double Stille–cyclisation (Scheme 4). The desired product was obtained in 28% yield, along with *ca.* 30% unreacted starting material, and *ca.* 30% of the iodostannane intermediate, which could itself be converted into the final product in *ca.* 60% yield.

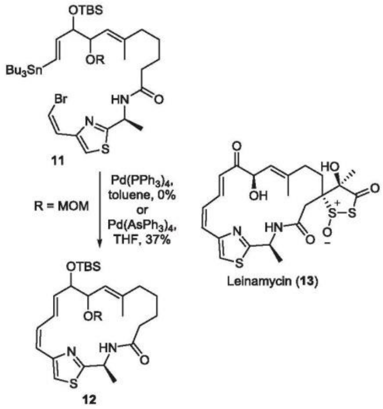
Rapamycin was subsequently also synthesised by Smith and co-workers using a single Stille reaction to close the ring, achieving a 74% yield for the cyclisation step.[34]

An important development for this type of approach to macrocyclic rings was reported by Farina and Krishnan in 1991.[35] They showed that the rate of Stille cross-coupling can be greatly enhanced by tuning the ligand around palladium, with the more labile $AsPh_3$ and $P(2\text{-}Fu)_3$ ligands offering the greatest enhancement

During the attempted cyclisation of their model system, **11**, they found that it could only be achieved using $AsPh_3$ as a ligand for Pd, and that the more classical PPh_3 system was ineffective, leading only to substrate decomposition (Scheme 5).

This methodology found use in elegant and efficient total syntheses of macrocyclic natural products throughout the 1990s and early 2000s. Prominent examples include macrolactins A[37–39] and E,[38] 14,15-anhydropristinamycin II_B[40,41] and sanglifehrin A.[42] Much of this work was reviewed by Pattenden and Duncton[43] in 1999 and so will not be covered in detail here. The extensive contributions to the field from his own group were also summarised by Pattenden in a subsequent review in 2002.[44]

Over the past decade, the Stille reaction has remained an important and widely used strategy for the synthesis of macrocyclic natural products, although it has perhaps faced increasing competition from other methods, alternative Pd-catalysed reactions being among them (vide infra). As can be seen from the examples



Scheme 5. Stille macrocyclisation catalysed by $Pd(AsPh_3)_4$ used in the synthesis of a model system of leinamycin (Pattenden and Thom, 1993)[36] (MOM=methoxymethyl, TBS=*tert*-butyldimethylsilyl).

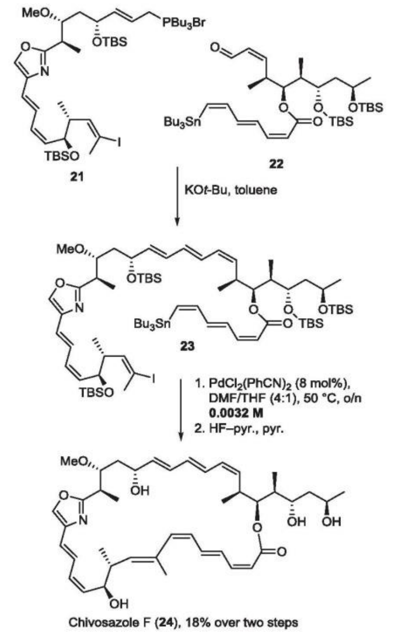
above, most early syntheses utilised an esterification or similar reaction to couple two large fragments, containing the appropriate functionality, prior to cyclisation via the Stille reaction.

This approach was frequently successful due to the mildness and efficiency with which the esterification can be employed. However, this also limited the application of the Stille reaction to macrolactones or macrolactams.

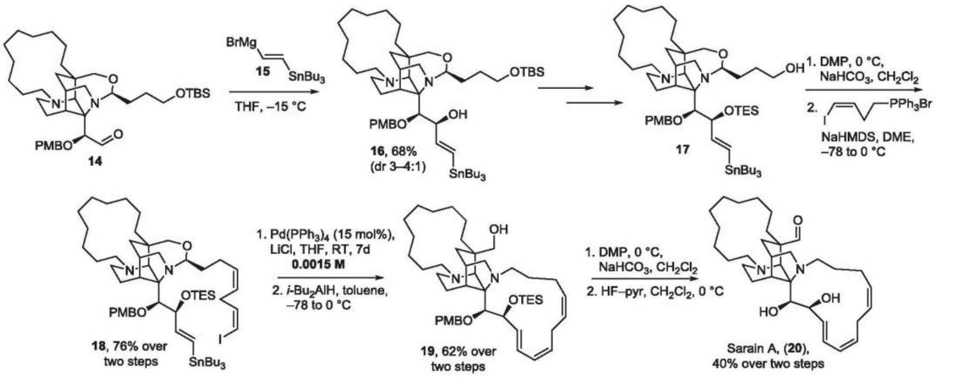
More recent syntheses have expanded beyond this strategy in order to target a range of natural products not necessarily containing an ester or amide linkage, and have used a variety of methods to introduce the required functionality for the Stille recation.

For example, in 2006 Overman reported the first total synthesis of the marine alkaloid (−)-sarain A (**20**), a structurally unique double macrocycle isolated from the Mediterranean sponge *Reniera sarai*.[45,46] A variety of methods were used to assemble the functionality required for the key Stille macrocyclisation (Scheme 6). The vinylstannane was introduced via an unusual Grignard reagent (**15**), and the vinyl iodide was introduced using a Wittig reaction as part of a skipped diene system. The macrocyclisation step then proceeded at room temperature with catalytic $Pd(PPh_3)_4$ and LiCl in a 62% yield over two steps, following reduction of the *N*,*O*-acetal.

The Wittig reaction has also been employed in the coupling of two large late-stage fragments directly before macrocyclisation. This strategy allows a highly convergent approach, with almost all the functionality installed in the two separate fragments before their coupling and cyclisation. An illustration of this was published by Kalesse and co-workers in their recent and first total synthesis of the 31-membered macrolide chivosazole F (**24**, Scheme 7).[47] Their approach allowed the assembly of the sensitive polyene units during the final stages of the total synthesis via a Wittig reaction between phosphonium salt **21** and aldehyde **22**. Stille



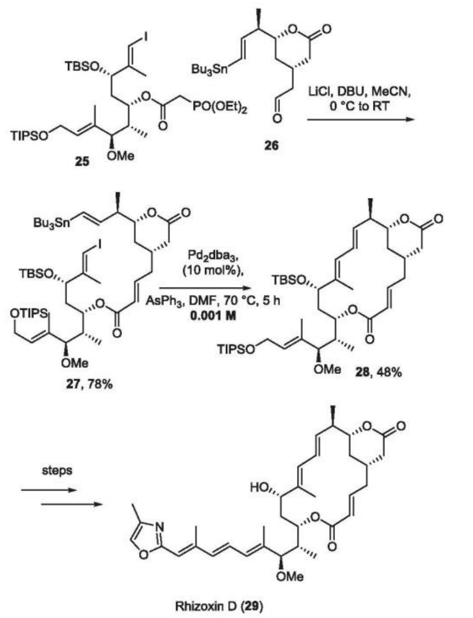
Scheme 7. Stille reaction used as a macrocyclisation strategy following a Wittig reaction in the first total synthesis of chivosazole F (Kalesse et al., 2010)[47] (pyr.=pyridine).



Scheme 6. Stille coupling used to form the second macrocyclic ring in the double macrocycle sarain A (Overman et al., 2006)[45] (DMP=Dess–Martin periodinane, PMB=*para*-methoxybenzyl).

macrocyclisation followed by global silyl deprotection completed the first total synthesis of chivosazole F.

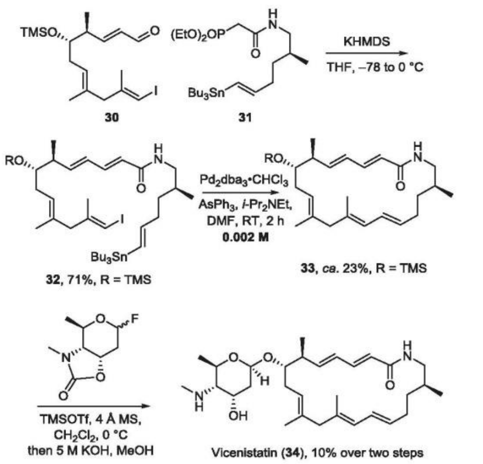
The Horner–Wadsworth–Emmons reaction has been used in a similar fashion to couple advanced and multi-functional intermediates immediately prior to Stille macrocyclisation. In a 2002 total synthesis of the antitumour compound rhizoxin D (**29**), Pattenden and co-workers employed this strategy to great effect (Scheme 8).[48,49] They were able to couple the phosphonate ester **25** with the aldehyde **26** under mild conditions, and follow this immediately with an intramolecular Stille reaction using a Pd_2dba_3/$AsPh_3$ catalyst system to form the 16-membered ring. Some minor functional group interconversions and addition of the side chain completed a concise and enantioselective total synthesis of the natural product in 0.45% overall yield.



Scheme 8. The use of a Stille macrocyclisation reaction in the total synthesis of rhizoxin D (Pattenden et al., 2002)[48] (dba=*E,E*-dibenzylideneacetone, DBU=1,8-diazabicyclo[5.4.0]undec-7-ene, TIPS=triisopropylsilyl).

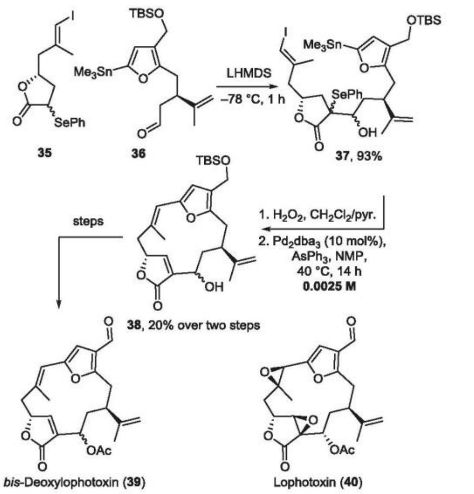
An analogous method has also been exploited by Kanoh and co-workers in their total synthesis of the cytotoxic glycoside vicenstatin (**34**), a 20-membered macrolactam isolated from *Streptomyces halstedii* HC-34, which shows promising anti-cancer properties.[50] They used a highly convergent route, again coupling the two fragments immediately prior to intramolecular Stille reaction using Pd_2dba_3, $AsPh_3$ and *i*-Pr_2NEt to effect the macrocyclisation (Scheme 9). The Horner–Wadsworth–Emmons reaction proceeded efficiently with both the phosphonate ester and the vinylstannane in the same molecule, demonstrating the stability and versatility of these types of fragments.

Pattenden and co-workers examined a similarly convergent approach during their 2005 studies towards the synthesis of *bis*-deoxylophotoxin (**39**), the likely biological precursor to the potent neurotoxin lophotoxin (**40**), isolated from the Pacific sea whip *Lophogorgia*. They used an innovative alkylation–elimination–macrocyclisation sequence via the selenide **37** to form the



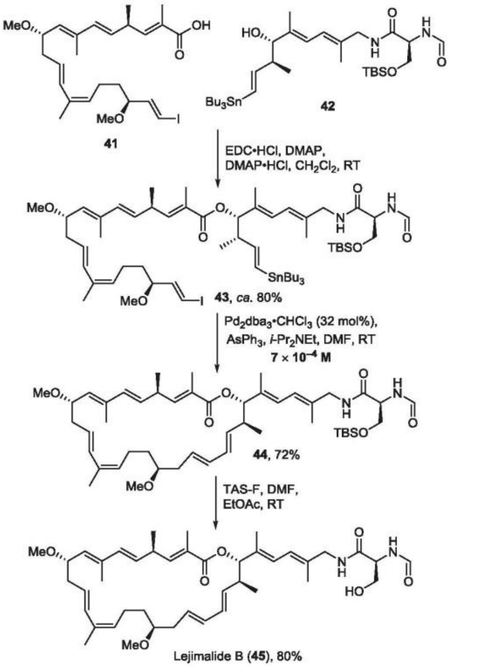
Scheme 9. Stille macrocyclisation following HWE reaction used in the total synthesis of vicenistatin (Kanoh et al., 2010)[50] (KHMDS=potassium hexamethyldisilazide, MS=molecular sieves, TMS=trimethylsilyl).

macrocyclic furanoterpene core (Scheme 10).[51,52] Paterson and co-workers used a very similar macrocyclisation approach in their concurrent studies towards lophotoxin.[53]



Scheme 10. Aryl–alkenyl Stille reaction as the macrocyclisation step in the total synthesis of *bis*-deoxylophotoxin (Pattenden et al., 2001)[51] (LHMDS=lithium hexamethyldisilazide).

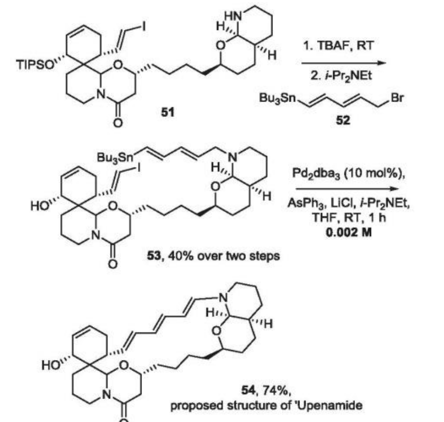
The methodology has also continued to prove itself valuable in the synthesis of macrocyclic amides and esters. Frequently the Stille reaction is favoured over macrolactonisation or macrolactamisation as the ring-closing step due to its mildness and reliability. This is illustrated by a recent synthesis by Helquist and co-workers of lejimalide B (**45**),[54] a 24-membered macrolide from *Eudistoma* cf. *rigida*, which has shown potent growth inhibition of human tumour cells. The natural product had been previously synthesised by both lactonisation[55] and ring-closing metathesis,[56,57] but Helquist's second generation synthesis utilised a highly convergent approach involving a late-stage intermolecular esterification followed by intramolecular Stille coupling in high yield, affording the natural product in a remarkable 19.5% overall yield over 15 linear steps (Scheme 11).



Scheme 11. Esterification followed by Stille macrocyclisation in the total synthesis of lejimalide B (Helquist et al., 2011)[54] (EDC=1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, DMAP=4-dimethylaminopyridine, TAS-F=tris(dimethylamino)sulfonium difluorotrimethylsilicate).

A recent synthesis by Bach and Ammer of the thopeptides amythiamicin C (**50**) and D, natural products which had again been previously synthesised by macrolactamisation,[58–60] demonstrates the mildness of the method.[61] Based on their previous successful synthesis of another macrocyclic peptide,[62,63] intermolecular Negishi and Stille reactions were used to build up two large and multifunctional fragments, **46** and **47**. These were coupled using an amide-bond formation, before undergoing a Stille macrocyclisation with $Pd(PPh_3)_4$ (Scheme 12). Amythiamicin C could thus be obtained in 5.8% overall yield over 11 linear steps.

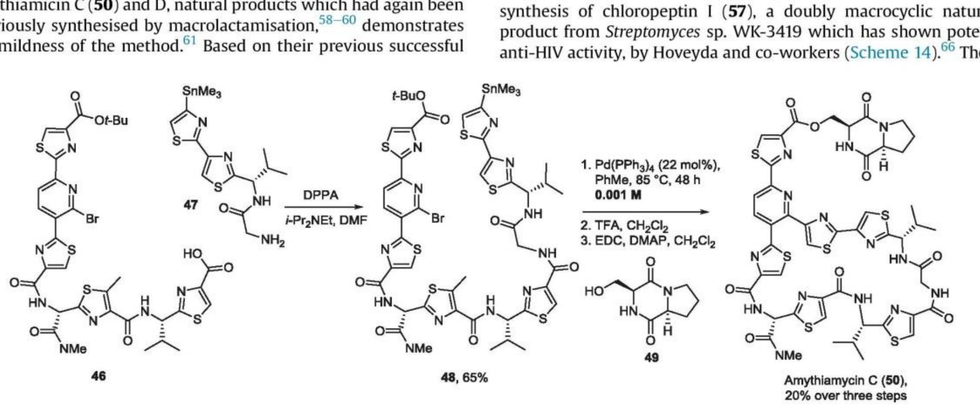
During their recent synthetic efforts towards 'upenamide, a macrocyclic marine alkaloid isolated from the Indonesian sponge *Echinochalina* sp., Taylor and co-workers utilised an intramolecular Stille reaction as the final step of their synthesis.[64] The required vinylstannane functionality was introduced as a conjugated diene (**52**) via an S_N2 reaction with a secondary amine (**51**). This was then cyclised using Pd_2dba_3 and $AsPh_3$ in excellent yield to give the target compound (**54**, Scheme 13).



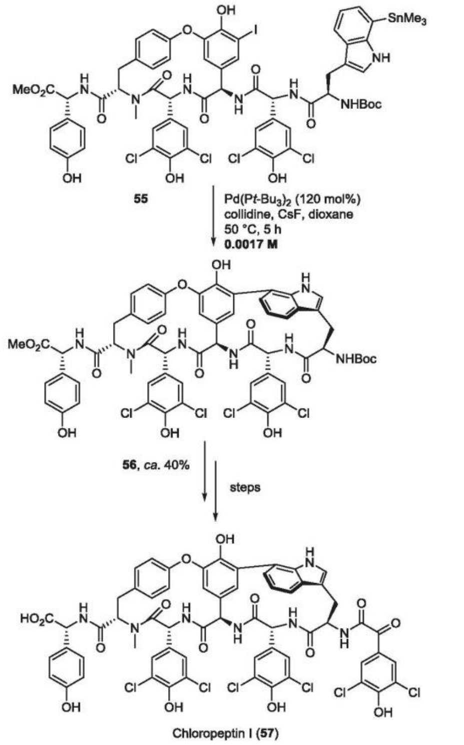
Scheme 13. Stille macrocyclisation as the final step in the total synthesis of the proposed structure of 'upenamide (Taylor et al., 2013).[64]

Unfortunately the spectroscopic data of **54** did not match that of natural 'upenamide, nor did that of an alternative diastereomer, synthesised using the same route. The correct structure of the natural product therefore remains uncertain.[65]

On occasion, aryl–aryl Stille coupling has been used as a macrocyclisation method, as illustrated by the first stereoselective total synthesis of chloropeptin I (**57**), a doubly macrocyclic natural product from *Streptomyces* sp. WK-3419 which has shown potent anti-HIV activity, by Hoveyda and co-workers (Scheme 14).[66] They



Scheme 12. Stille macrocyclisation following amide-bond formation in the total synthesis of amythiamycin C (Bach and Ammer, 2010)[61] (DPPA=diphenylphosphoryl azide, TFA=trifluoroacetic acid).

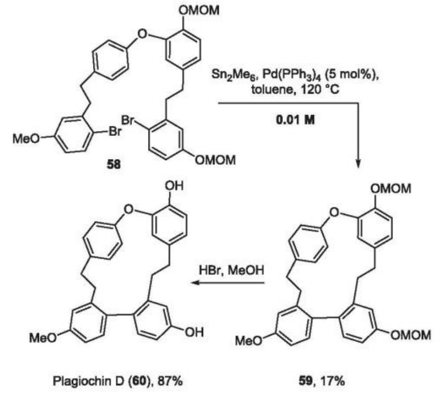


Scheme 14. Aryl–aryl Stille coupling used as a macrocyclisation in the total synthesis of chloropeptin I (Hoveyda et al., 2003).[66]

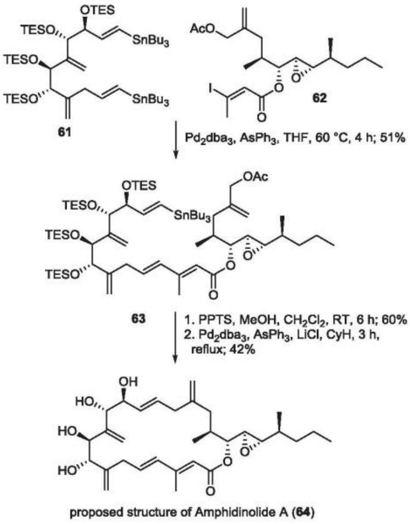
note that the addition of collidine (10 equiv.) is essential for the efficiency of the reaction, suggesting that it might stabilise the active Pd complex. By combining this with $Pd(Pt\text{-}Bu_3)_2$ and CsF in dioxane, they are able to isolate the desired macrocycle in *ca.* 40% yield.

An earlier variation of this method was reported by Fukuyama and co-workers in their total syntheses of the 16-membered *bis*(-bibenzyl) natural products plagiochins D (**60**)[67] and A.[68] This involved treating dibromide **58** with hexamethylditin and a palladium source, $Pd(PPh_3)_4$, effecting stannylation and cyclisation in one pot (Scheme 15). Along with the product **59**, which was isolated in 17% yield, they also recovered the mono-stannylated product (which underwent cyclisation itself in 20% yield) along with unreacted starting material (45%).

Whilst most of the Stille macrocyclisations outlined above involve the sp^2–sp^2 coupling of a vinyl- or arylstannane with a vinyl or aryl halide, the Stille reaction can also be used effectively for sp^2–sp^3 couplings in the case of allylic or benzylic electrophiles. The first example of a Stille coupling used in this way for a macrocyclisation reaction was published by Pattenden and Lam during studies towards the total synthesis of the 20-membered macrolactone amphidinolide A (Scheme 16). They showed the feasibility of this approach, first in a model system,[69] and subsequently in the total synthesis of the presumed structure of the natural product (**64**).[70] In a remarkable display of selectivity, they used an intermolecular Stille cross-coupling to unite two late-stage fragments **61** and **62**, relying on the greater reactivity of the vinyl iodide over



Scheme 15. One-pot cyclisation of dibromide **58** with Sn_2Me_6 and $Pd(PPh_3)_4$ in the total synthesis of plagiochin D (Fukuyama et al., 1999).[67]

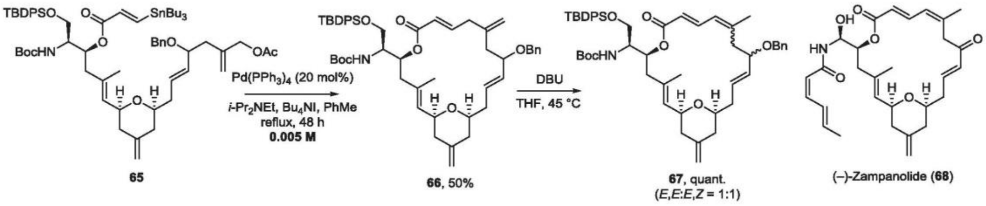


Scheme 16. Use of the π-allyl Stille macrocyclisation as the final step in the total synthesis of the proposed structure of amphidinolide A (Pattenden and Lam, 2002)[70] (PPTS=pyridinium *p*-toluenesulfonate, TES=triethylsilyl).

the allylic acetate to facilitate reaction with the less hindered vinyl stannane. Global deprotection was followed by an intramolecular Stille cross-coupling with the allylic acetate to afford the macrocycle in good yield. Interestingly during their model studies they found that relatively non-polar solvents such as cyclohexane gave the best yields, regio- and stereoselectivities, contrasting with the polar aprotic solvents which are frequently employed for the Stille reaction. A comparison of the NMR spectroscopic data of the final compound with those reported for amphidinolide A showed that the authors had in fact prepared a diastereomer of the natural product, leading to a revision of the proposed structure. An alternative diastereomer synthesised in an identical fashion also did not match the data for the natural compound.

An interesting adaptation of this technique was demonstrated by Porco Jr. and co-workers in their preparation of the macrocyclic core of the 20-membered macrolide (−)-zampanolide (**68**), a cytotoxic natural product from the Okinawan sponge *Fasciospongia rimosa*.[71] In an effort to assemble the potentially sensitive 1,3-dienoate at a late stage of the total synthesis, they carried out the macrocyclisation of precursor **65** with catalytic $Pd(PPh_3)_4$, *i*-Pr_2NEt and Bu_4NI in toluene to afford a 1,4-dienoate (**66**) in 50% yield; this was then isomerised to the conjugated diene **67** quantitatively with DBU (Scheme 17).

This reaction as a macrocyclisation method subsequently received little attention until White and co-workers' key total synthesis in 1998 of rutamycin B (**74**), a 26-membered macrocyclic antibiotic isolated from *Streptomyces aureofaciens*.[73,74] They introduced the boron-containing functional group at a late stage of the synthesis, this time using a recently reported chromium-mediated transformation (Scheme 19).[75] The resulting vinylboronate was then coupled with the pre-installed vinyliodide using

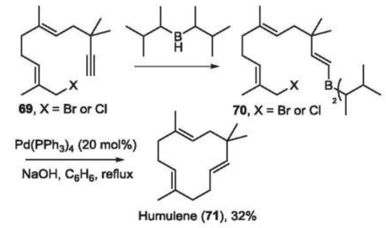


Scheme 17. Use of an intramolecular π-allyl Stille coupling followed by base-mediated isomerisation in the synthesis of the macrocyclic core of (−)-zampanolide (Porco Jr. et al., 2008)[71] (TBDPS=*tert*-butyldiphenylsilyl).

4. The Suzuki–Miyaura reaction

The Suzuki–Miyaura reaction has found extensive use in the total synthesis of macrocyclic natural products. Unlike the Stille coupling, mainly used for vinyl–vinyl couplings, the Suzuki reaction has also frequently been used for aryl–aryl or aryl–vinyl macrocyclisations.

The first reported macrocyclisation using this methodology was by Miyaura and co-workers in their 1984 total synthesis of the sesquiterpene natural product humulene (**71**, Scheme 18), an 11-membered macrocyclic hydrocarbon.[72] Their approach involved a late-stage hydroboronation of terminal alkyne **69**, followed by a coupling with the allylic bromide or chloride using $Pd(PPh_3)_4$ under basic conditions. In both cases, the natural product was detected by GLC in a 32% yield.

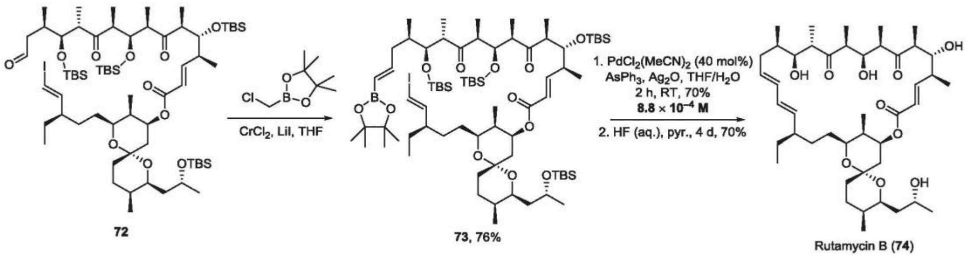


Scheme 18. First reported use of the Suzuki–Miyaura coupling as a macrocyclisation reaction, used in the total synthesis of humulene (Miyaura et al., 1984).[72]

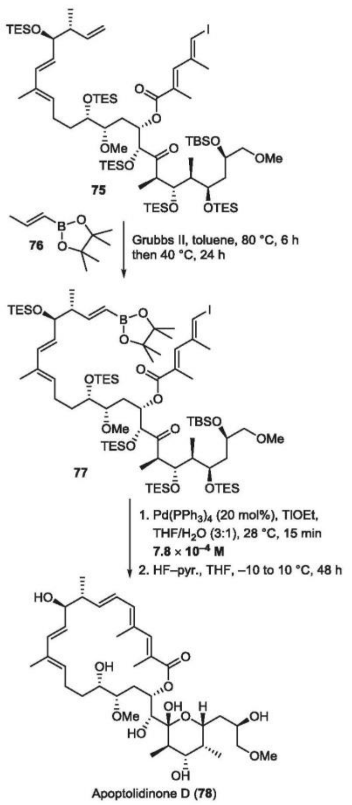
$PdCl_2(MeCN)_2$, $AsPh_3$ and Ag_2O in THF to form the macrocyclic ring in high yield. Desilylation with HF–pyridine afforded the natural product.

Since then, the Suzuki reaction has been widely employed as a tool for macrocyclisation. Sulikowski and co-workers used it in their syntheses of both apoptolidinones A and D (Scheme 20).[76,77] These synthetic compounds are the aglycones of apoptolidins A and D, secondary metabolites from *Nocardiopsis* sp., and share a common 20-membered macrocyclic core. They were targeted in order to assess their biological activity compared to the apoptolidins, which have been shown to be selectively cytotoxic against a number of cancer cell lines. Their strategy for both targets was to introduce the vinylboronate at a late stage in the synthesis via a cross-metathesis reaction with vinylboronate **76** using Grubbs' second-generation catalyst. The resulting cyclisation precursor **77** then underwent efficient intramolecular cross-coupling in the presence of $Pd(PPh_3)_4$ and TlOEt to close the macrocyclic ring. Global desilylation with concomitant lactonisation then afforded the target compounds.

Another elegant illustration of the efficacy of this method was reported by Roush and co-workers in their 2008 synthesis of (+)-superstolide A (**82**).[78,79] Their approach to this tricyclic 16-membered cytotoxic macrolide was to first target the 24-membered macrocyclic octaene **80** before conducting an intramolecular Diels–Alder reaction to form the tricyclic core (Scheme 21). Their macrocyclisation proceeded efficiently at room temperature using catalytic $Pd(PPh_3)_4$ and TlOEt; the subsequent transannular Diels–Alder reaction could either be effected at room temperature over five days or by heating in toluene to 80 °C for 2 h. This allowed the construction of the macrocyclic core of



Scheme 19. Intramolecular Suzuki coupling as the penultimate step in the total synthesis of rutamycin B (White et al., 1998).[73]

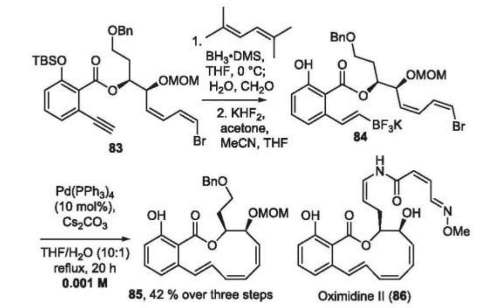


Scheme 20. Suzuki coupling of a pinacol boronate to effect macrocyclisation in the total synthesis of apoptolidinone D (Wu et al., 2004).[76]

superstolide A in 30–35% yield over two steps; a further four steps furnished the target compound, the spectroscopic properties of which were in complete agreement with the data from the natural product.

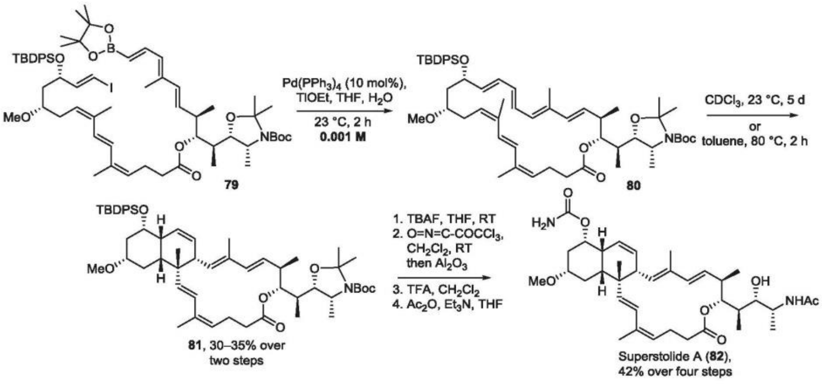
In addition to the more commonly employed boronic esters, potassium organotrifluoroborates can also act as effective coupling partners during macrocyclisation. This was first demonstrated by Molander's formal total synthesis of oximidine II (**86**), a cytotoxic 12-membered macrolactone from *Pseudomonas* sp.[80]

The trifluoroborate functional group was introduced directly before the macrocyclisation step, which was achieved with $Pd(PPh_3)_4$ and Cs_2CO_3 in wet THF in a good yield over three steps (Scheme 22). An alternative route reported in the same paper involving Suzuki cross-coupling prior to a macrolactonisation step was unsuccessful due to the steric strain inherent in the 12-membered system.

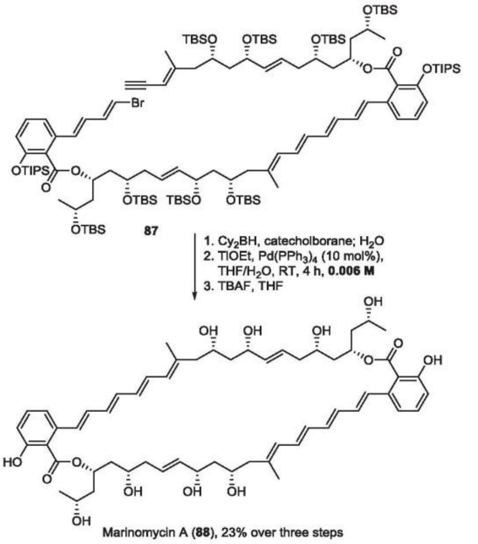


Scheme 22. Suzuki macrocyclisation reaction using a trifluoroborate couling partner in the total synthesis of oximidine II (Molander and Dehmel, 2004).[80]

In their impressive syntheses of the 44-membered marinomycins A–C, potent antibiotics from the marine actinomycete *Marinispora*, Nicolaou and co-workers attempted a dimerisation approach, whereby the two symmetric halves of the molecule could be joined in a tandem dimerisation–macrocyclisation reaction.[81] Ultimately this proved unsuccessful, with cyclisation to the monomeric macrocycle ('monomarinomycin') dominating, despite the reaction being tested at a range of concentrations (1.0–0.005 M). A similar attempt with a Heck coupling led to comparable results, whilst a Stille stitching cyclisation was also ineffective. The successful synthesis of **88** necessitated a stepwise approach, with a Suzuki coupling followed by a Mitsunobu reaction joining the various fragments (Scheme 23). A hydroboronation of a terminal alkyne (**87**) followed directly by a Suzuki



Scheme 21. Suzuki macrocyclisation followed by a transannular Diels–Alder reaction in the total synthesis of superstolide A (Roush et al., 2008).[78]



Scheme 23. Hydroboronation followed by Suzuki macrocyclisation in the total synthesis of marinomycin A (Nicolaou et al., 2007).[81]

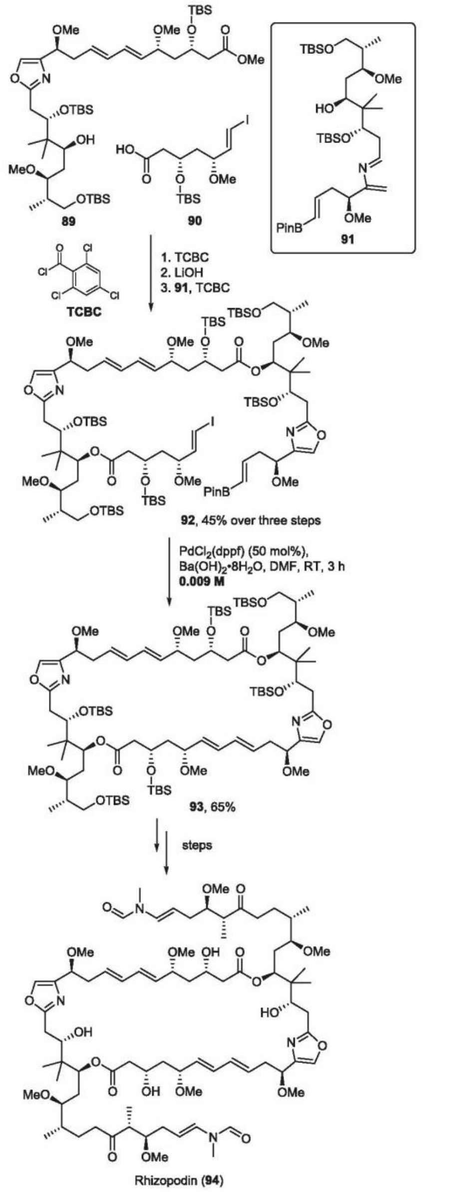
macrocyclisation and silyl deprotection afforded the marinomycin A (**88**) in 23% yield over three steps.

Whilst the required boron-containing functional groups are often introduced into the molecule at a late stage, immediately prior to macrocyclisation, in order to avoid any possible side reactions, fragment-based approaches have also been used. This involves the coupling of two elaborated fragments whereby the required functional groups for macrocyclisation are already installed. An example of this is found in Menche and co-workers' recently reported total synthesis of the 38-membered macrolide rhizopodin (**94**), a potent cytotoxin isolated from the myxobacterium *Myxococcus stipitatus*.[82] They used the Yamaguchi esterification to unite three advanced fragments (**89**, **90** and **91**) before a Suzuki macrocyclisation afforded their 38-membered ring (**93**) in good yield (Scheme 24). Introduction of the labile side chains and deprotection provided the natural product in 31 linear steps.

One area where the Suzuki macrocyclisation has been particularly successful is when cyclisation requires an aryl–aryl or aryl–alkenyl bond formation. Aryl boronic acids and esters are very widely used reagents, which readily undergo Suzuki coupling with a variety of aryl and alkenyl halides, and this reactivity can be exploited when a biaryl moiety is embedded within the macrocyclic ring.

An early report by Elder and Rich demonstrated the feasibility of this strategy as a macrocyclisation method during their studies towards the DEF ring systems of the natural products chloropeptin I (**57**, Scheme 14) and complestatin (chloropeptin II, **90**), both isolated from *Streptomyces* sp. WK-3419.[83] They found that conducting an amide coupling between two fragments, **95** and **96**, followed by an intramolecular Suzuki coupling gave the 17-membered ring system (**98**) is good yield (Scheme 25). This was found to be superior to the alternative involving an intermolecular Suzuki reaction followed by a macrolactamisation, which afforded the product in only 43% yield.

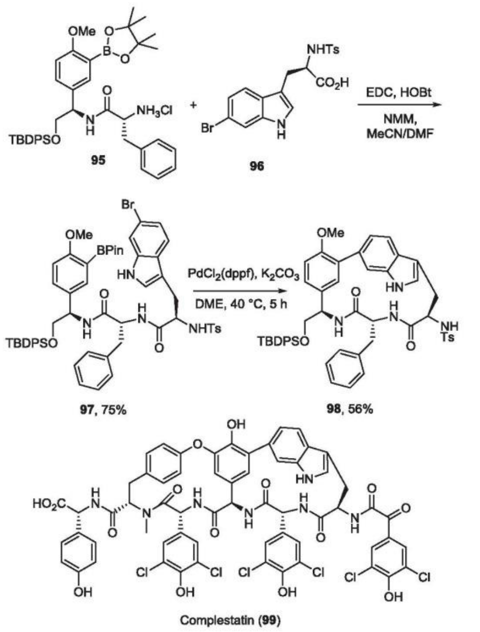
Complestatin (**99**) itself, and its closely related isomer chloropeptin I (**57**), were later synthesised by Zhu and co-workers using this approach,[84,85] as was the unnatural (*S*)-atropisomer isocomplestatin by Hoveyda and co-workers.[86] Other natural products



Scheme 24. Suzuki macrocyclisation following two Yamaguchi ester couplings in the total synthesis of rhizopodin (Menche et al., 2012).[82]

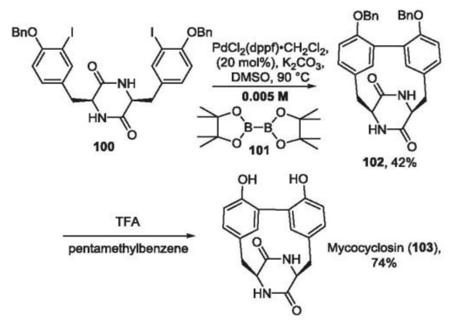
synthesised using this strategy include isoplagiochin D[87] and riccardin C (along with seven methylated analogues)[88] by Fukuyama, arylomycin A_2 by Romesberg[89] and Zhu,[90] and biphenomycin B,[91] RP-66453[92] and arylomycin B_2[90] by Zhu.

An interesting adaptation of this strategy was reported by Hutton and co-workers in their first total synthesis of mycocyclosin



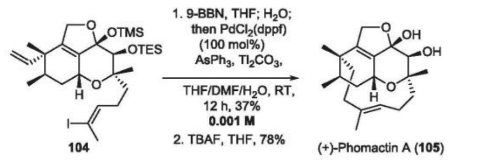
Scheme 25. Demonstration of the feasibility of an aryl–aryl Suzuki macrocyclisation in the synthesis of the DEF ring of chloropeptin I and complestatin (Elder and Rich, 1999)[83] (HOBt=hydroxybenzotriazole, NMM=*N*-methylmorpholine).

(**103**), a 12-membered macrocyclic diketopiperazine isolated from *Mycobacterium tuberculosis*.[93] Originally developed by Zhu,[94] the method involves forming the desired cyclisation precursor in situ from a readily synthesised diiodide such as **100**. On heating this precursor with the diboron ester **101**, K_2CO_3 and catalytic $Pd(dppf)_2Cl_2$, they were able to isolate the desired macrocycle **102** in 42% yield; subsequent debenzylation with TFA afforded the natural product target (Scheme 26).



Scheme 26. One-pot cyclisation of diiodide **100** in the total synthesis of mycoclosin (Hutton et al., 2012).[93]

The *B*-alkyl Suzuki reaction is a valuable method, which can be used to construct sp^2–sp^3 bonds. It involves hydroboronation of a terminal alkene (normally with 9-BBN), followed by a Pd-catalysed cross-coupling with an aryl or alkenyl electrophile. This reaction holds much potential for natural product total synthesis as, in theory, it allows a disconnection adjacent to any alkyl-substituted alkene. The application of this concept to a macrocyclisation was initially reported simultaneously by Halcomb[95] and Danishefsky,[96] as a potential methodology for the synthesis of the phomactins, a family of diterpenes isolated from the marine fungus *Phoma* sp. Halcomb and co-workers subsequently employed this successfully in their total synthesis of (+)-phomactin A (**105**).[97] The macrocyclisation step was achieved in 37% yield using $Pd(dppf)Cl_2$, $AsPh_3$ and Tl_2CO_3 (Scheme 27).

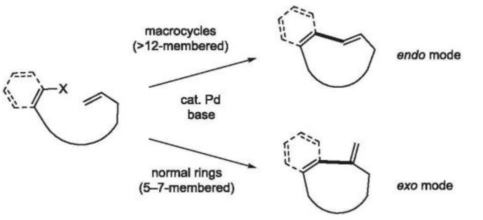


Scheme 27. *B*-alkyl Suzuki cyclisation in the total synthesis of (+)-phomactin A (Halcomb et al., 2003)[97] (9-BBN=9-borabicyclo(3.3.1)nonane).

Maier has also used this strategy in the synthesis of the core structure of salicylhalamine A,[98] and Danishefsky has further explored the methodology in work towards the total synthesis of xestocyclamine A.[99]

5. The Heck reaction

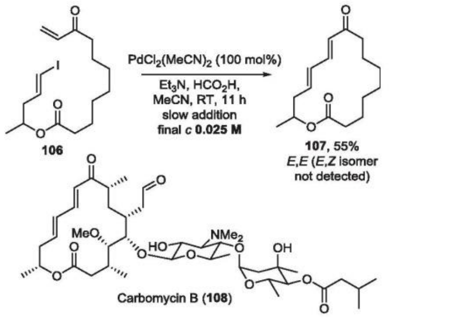
The Heck reaction was one of the first Pd-catalysed carbon–carbon bond forming reactions to be discovered, and has since found extremely wide use in organic synthesis. In an intramolecular sense, the Heck reaction can proceed to give one of two different products as a result of *endo*- or *exo*-cyclisation (Scheme 28).[100] Whilst the *endo*-cyclisation is more thermodynamically favoured, affording the more stable substituted alkene, it is also more sterically demanding. In general therefore, normal and medium ring sizes favour *exo*-cyclisation, whilst macrocyclisations generally proceed via the *endo*-pathway, with high (often complete) selectivity for the more thermodynamically stable *E*-alkene.



Scheme 28. Two different cyclisation modes for the intramolecular Heck reaction, dependent on ring size of the resultant cycle.

The first application of the Heck cyclisation to a macrocyclic substrate was reported by Zeigler and co-workers in 1981 during their studies towards the total synthesis of carbonolide B, the aglycone of the macrocyclic antibiotic carbomycin B (**108**).[101] They achieved the cyclisation to the model substrate **107** in 55% yield, by slow addition to a solution of $PdCl_2(MeCN)_2$, Et_3N and formic acid in MeCN at ambient temperature (Scheme 29).

Following this initial report, the area received relatively little attention, with only sporadic examples of Heck macrocyclisations being reported in the following two decades.[102–104] More recently the intramolecular Heck reaction has emerged as a useful methodology for the synthesis of macrocycles in natural products. In their 2009 formal total synthesis of the cytotoxic macrolide palmerolide A (**112**), Maier and Jägel found that the Heck cyclisation afforded better yields



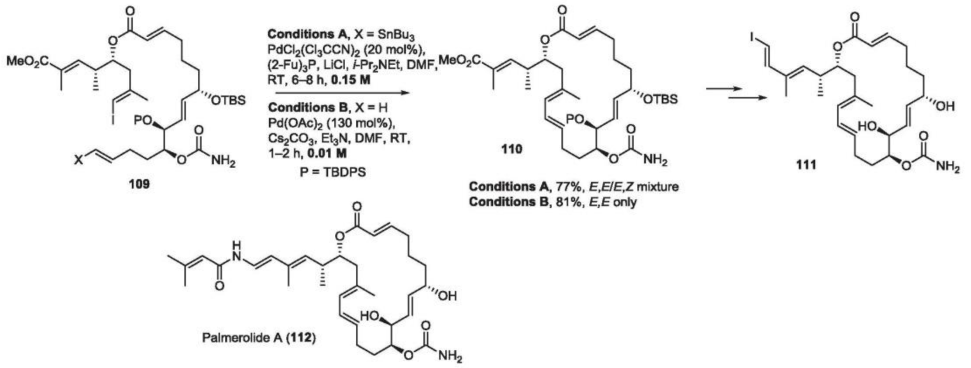
Scheme 29. First reported Heck macrocyclisation, as used in a model system towards carbomycin B (Zeigler et al., 1981).[101]

and stereoselectivity than the rather more popular Stille reaction, although it required non-catalytic quantities of an unusual palladium precatalyst, $PdCl_2(Cl_3CCN)_2$ (Scheme 30).[105] This strategy allowed them rapid access to compound **111**, an advanced intermediate in the synthetic route reported by Nicolaou, Chen and co-workers.[106,107]

In 2010, Spivey and co-workers reported the total synthesis of the fungal metabolite (±)-aspercyclide A (**126**).[115] They initially found that a competing direct-arylation-type process was more favourable than their desired Heck macrocyclisation (Scheme 33). They were able to suppress the formation of the byproduct by the addition of stoichiometric AgI, giving halogen exchange to the aryl iodide and allowing them isolation of the desired product **123** in 52% yield. Interestingly, a hydroxyl protecting group switch from Me to PMB completely avoided the unwanted byproduct, even without the addition of AgI. The authors were subsequently able to apply the same route to the enantioselective total synthesis of (+)-aspercyclide (**126**).[116]

Speicher and co-workers recently reported the first application of a Heck macrocyclisation to a *bis*(bibenzylic) natural product, isoplagiochin D (**129**).[117] By using an *M*-BINAP ligand, they were able to obtain their cyclised compound **128** with a moderate selectivity (37% ee) for one atropisomer, albeit in low (22%) yield (Scheme 34). Reduction of the alkene and deprotection afforded the natural product.

An interesting reversal of selectivity was published by Ojima and co-workers in their studies of the bioactive conformation of paclitaxel and its congeners.[118] Intriguingly, they found that when compounds **130** and **132** were cyclised, under standard conditions,



Scheme 30. Comparison of Stille (conditions A) and Heck (conditions B) macrocyclisation reactions in the formal total synthesis of palmerolide A (Maier and Jägel, 2009).[105]

Similarly Menche and co-workers used a Heck macrocyclisation during their total synthesis of the 24-membered macrolactone archazolid B (**118**).[108] They found that this strategy afforded a better yield (41% over three steps) than an alternative Horner–Wadsworth–Emmons (HWE) strategy used in their synthesis of the related macrocycle archazolid A (**116**) (25% over three steps) (Scheme 31).[109] The archazolids are potent V-ATPase inhibitors, and both syntheses were achieved by divergence of late-stage joint intermediates **113** and **114**.

Menche has also used this strategy in the synthesis of the macrocyclic core of rhizopodin (**94**),[110] as a considerable improvement upon his Suzuki-macrocyclisation-based approach[82] (Scheme 24), and the total synthesis of the potent antibiotic etnangien (**121**).[111,112] In this latter case, the key Heck macrocyclisation of **119** with $Pd(OAc)_2$, K_2CO_3 and Bu_4NCl was found to be more efficient than either lactonisation or ring-closing metathesis, furnishing the 22-membered macrocycle **120** in an impressive 70% yield (Scheme 32). Menche and Irschik later extended this investigation, using a similar method to generate a range of simplified analogues for structure–activity relationship studies.[113] Kalesse and Symkenberg also used an analogous approach in their very recent total synthesis of kulkenon.[114]

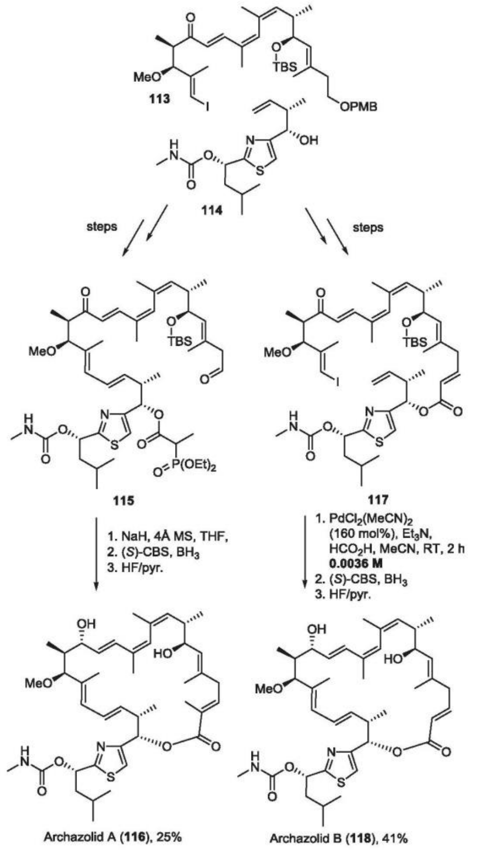
exo-selectivity was observed. Switching the iodide and olefin moieties led to either a mixture of *endo*- and *exo*-products, or complete *endo*-selectivity. An attempt with a larger ring also gave complete *endo*-selectivity (Scheme 35).

6. The Sonogashira reaction

Whilst it has found some use in the synthesis of macrocyclic peptides[119,120] and rigid synthetic ring systems,[121–126] the Sonogashira reaction has found comparatively little use in the synthesis of macrocyclic natural products, presumably due to the paucity of natural ring systems containing conjugated alkynes.

An early and elegant example was reported by Schreiber and co-workers in their studies towards structural variants of the antitumour natural product dynemicin A (**137**).[127] They used an intramolecular Sonogashira reaction to form a 15-membered ring, which, rather than forming the expected macrolactone **135**, underwent an in situ transannular Diels–Alder reaction to compound **136** (Scheme 36).

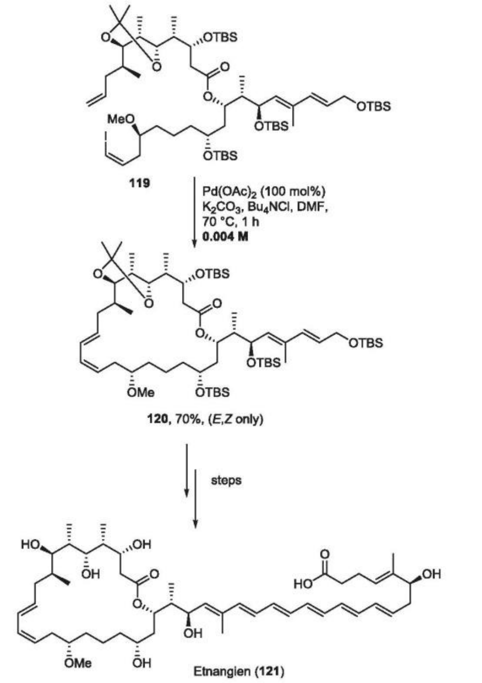
Another impressive example is found in the synthesis of the ansamacrolide of kedarcidin chromophore (**140**) by Hirama and co-workers.[128] Whilst their initial studies had afforded only moderate



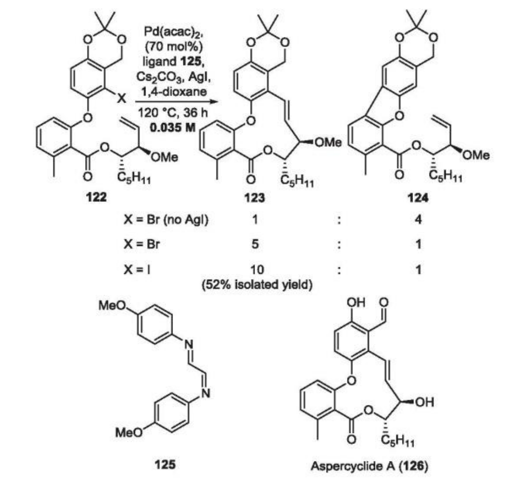
Scheme 31. Comparison of HWE and Heck macrocyclisation approaches in the total syntheses of archazolids A and B (Menche et al., 2009)[108] (CBS=Corey–Bakshi–Shibata reagent).

yields of the analogous C4-epimer of **139**,[129] careful selection of protecting groups led to the isolation of the macrocycle in a remarkable 88–90% yield (Scheme 37). Whilst they were subsequently able to complete the synthesis of the carbon framework of the aglycone of the natural product using this methodology, late-stage introduction of the epoxide proved problematic, and the eventual total synthesis of a protected version of the aglycone was achieved using a macrolactonisation reaction.[130]

A powerful illustration of the utility of the Sonogashira macrocyclisation in the synthesis of large-ring macrocycles was reported by Mohapatra and co-workers in their first total synthesis of penarolide sulfate A_1 (**144**), an α-glucosidase inhibitor isolated from the marine sponge *Penares* sp.[131] Whilst the final natural product contains no alkyne or even alkene functionalities, the reliability of the Sonogashira reaction was employed to form the 30-membered macrocycle from compound **141** (Scheme 38). The macrocyclisation step was achieved at a remarkably high concentration (0.22 M) with catalytic $Pd(PPh_3)_4$ and CuI in Et_2NH in just 30 min at room temperature. The resulting eneyne was simply reduced out using Raney Ni; a global deprotection and three-step persulfation protocol then completed the first total synthesis of the natural product in high yield.



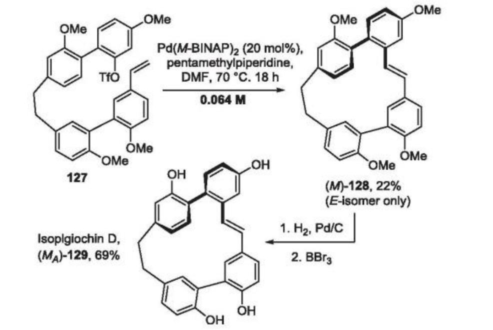
Scheme 32. An efficient Heck coupling used to effect macrocyclisation in the total synthesis of etnangien (Menche et al., 2009).[111]



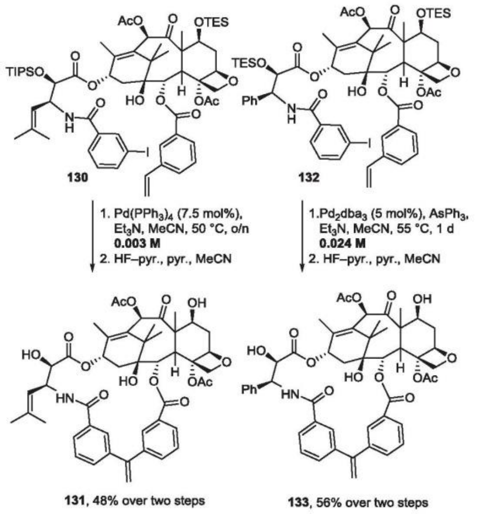
Scheme 33. Optimisation of conditions for efficient Heck macrocyclisation towards the total synthesis of aspercyclide A (Spivey et al., 2010).[115]

7. The Tsuji–Trost reaction

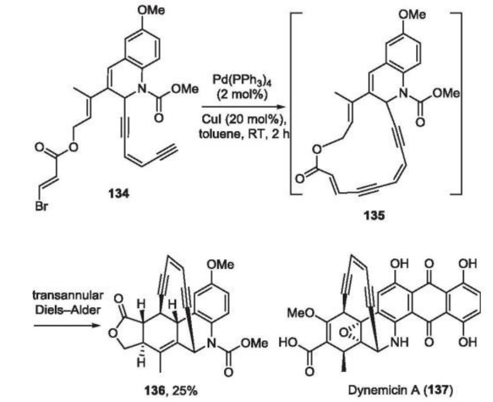
As in the Heck cyclisation, the intramolecular reaction between a nucleophile and an allylic electrophile presents the possibility of



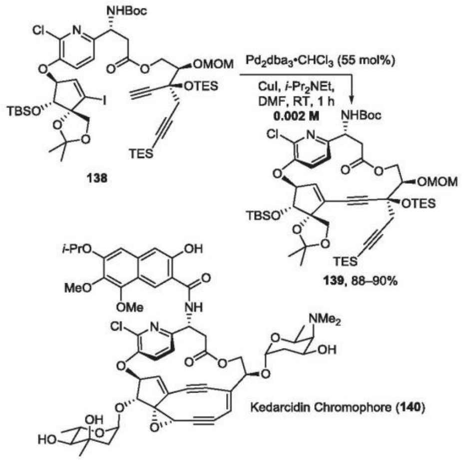
Scheme 34. Atroposelective Heck macrocyclisation in the total synthesis of isoplagiochin D using Pd(*M*-BINAP)$_2$ (Speicher et al., 2012)[117] (BINAP=2,2′-bis(diphenylphosphino)-1,1′-binaphthyl).



Scheme 35. *Exo*-selective Heck macrocyclisations observed during studies on paclitaxel and its congeners (Ojima et al., 2003).[118]



Scheme 36. An early example of the Sonogashira reaction used as a macrocyclisation step followed by an intramolecular Diels–Alder reaction in the total synthesis of dynemicin A (Schreiber et al., 1990).[127]



Scheme 37. Use of the Sonogashira macrocyclisation in an attempted total synthesis of kedarcidin chromophore (Hirama et al., 2005).[128]

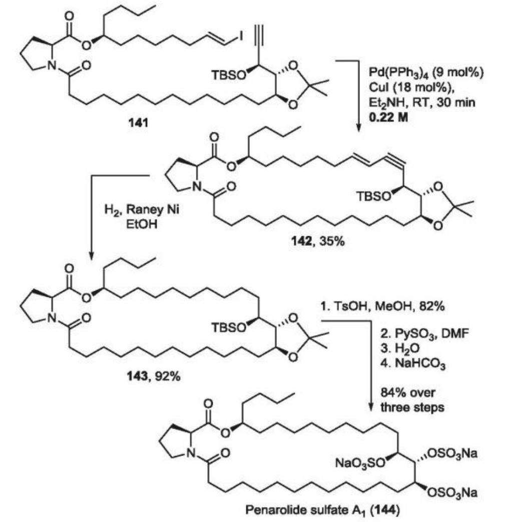
forming two isomeric rings with a difference in ring size of two atoms.[132] Whilst the ratio of these two products depends on a variety of factors, and in smaller ring systems (4–9 membered) mixtures are possible, in larger systems (>10 membered) terminal substitution appears to dominate, corresponding to the larger ring size.

Having been one of the first Pd-catalysed coupling reactions to be developed in the late 1960s, allylic acetate coupling was also the earliest to be used as a macrocyclisation reaction. In consecutive reports, Yamamoto[133] and Trost[134] both employed this strategy in the total synthesis of 11-membered humulene (**71**) and 16-membered exaltolide (**149**), respectively (Scheme 39). Yamamoto used a β-ketoester to form the required enolate, whilst Trost used the more acidic sulfonyl compound **147**, and achieved a higher yield.

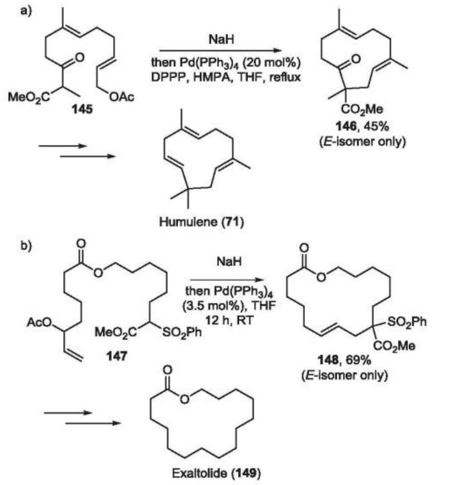
Yamamoto found that of 1,3-bis(diphenylphosphino)propane (DPPP) was the most efficient ligand for the macrocyclisation, and this was later explored and expanded upon by Trost in his subsequent synthesis of the antibiotic natural product A26771B (**152**, Scheme 40).[135] It was found that DPPP or 1,4-bis(diphenylphosphino)butane (DPPB) both worked equally effectively, but that two equivalents of 1,2-bis(diphenylphosphino)ethane (DPPE) relative to the palladium led to no cyclisation. This was attributed to the catalytically inactive ‘Pd(dppe)$_2$’ species, which has a high stability with respect to ligand dissociation, forming under the reaction conditions; when the number or equivalents with respect to the palladium was reduced to 1.05, the product could be isolated in 59% yield. The need to rigorously exclude oxygen in order to achieve a successful reaction was also noted.

This synthetic approach to macrocycles was soon frequently being applied to the total synthesis of more complex natural products. Key examples include (±)-recifeiolide,[136] inandenin-12-one,[137] and (−)-aspochalasin B[138] by Trost, and isolobophytolide[139] by Lebioda. Trost neatly summarised much of this work as well as his own extensive contribution to the field in a review in 1989.[132]

The methodology has continued to find use in more recent years as a macrocyclisation strategy in natural product total synthesis. It



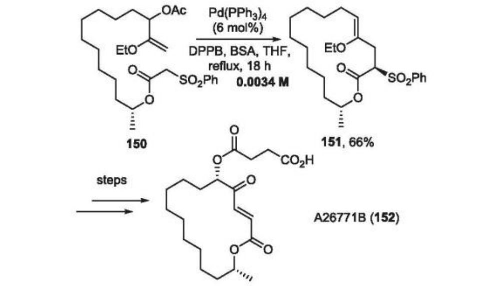
Scheme 38. Sonogashira reaction used in the macrocyclisation of the large-ring natural product penarolide sulfate A_1 (Mohapatra et al., 2008).[131]



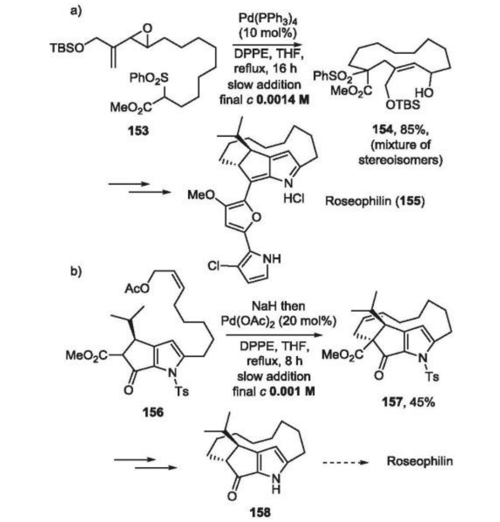
Scheme 39. First examples of a Tsuji–Trost macrocyclisation reaction in the synthesis of a) humulene (Yamamoto et al., 1977)[133] and b) exaltolide (Trost and Verhoeven, 1977)[134] (DPPP=1,3-bis(diphenylphosphino)propane).

has been employed in the total synthesis of the potent cytotoxic agent roseophilin (**155**), firstly by Fürstner and Weintritt,[140] and later by Frontier and Bitar[141] in their formal total synthesis (Scheme 41). Whilst Fürstner formed the macrocyclic ring early on in the synthesis using a vinyl oxirane moiety (**153**), Frontier employed a late-stage macrocyclisation using allylic acetate **156**. Both found DPPE to be the most effective ligand for the macrocyclisation step.

Whilst a base is normally employed in these types of reactions in order to generate the carbon-based nucleophile to attack the π-allyl Pd complex, other more innovative nucleophiles can also be used. For example, in their total syntheses of both δ-araneosene (**161**) and



Scheme 40. Use of a bidentate phosphine ligand for the Tsuji–Trost macrocyclisation of A26771B (Trost and Brickner, 1983)[135] (BSA=bis(trimethylsilyl)acetamide).

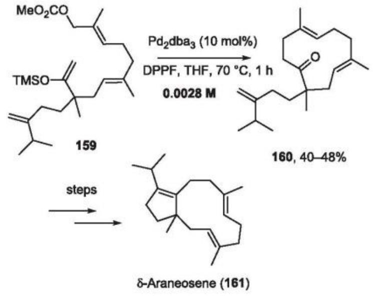


Scheme 41. Alternative Tsuji–Trost macrocyclisation-based approaches to the natural product roseophilin using a) a vinyl oxirane (Fürster and Weintritt, 1998)[140] and b) an allylic acetate (Frontier and Bitar, 2008).[141]

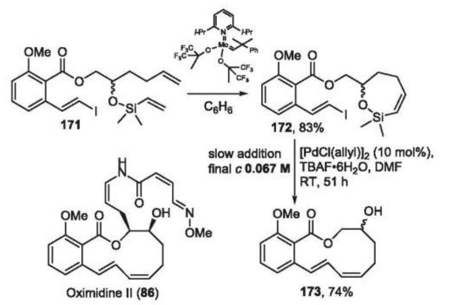
humulene (**71**), Corey and Hu utilised a silyl enol ether (**159**) to couple with a π-allyl complex generated from an allylic carbonate, apparently the first cyclisation of this type (Scheme 42).[142]

The analogous cyclisation step in the synthesis of humulene was achieved in a similar 44–52% yield under identical conditions. A very recent report on the total synthesis of kendomycin by Arimoto and co-workers describes the use of a Tsuji–Trost macro-etherification reaction, employing a phenol nucleophile, followed by a Claisen rearrangement to construct the 16-membered carbocyclic core of the natural product.[143]

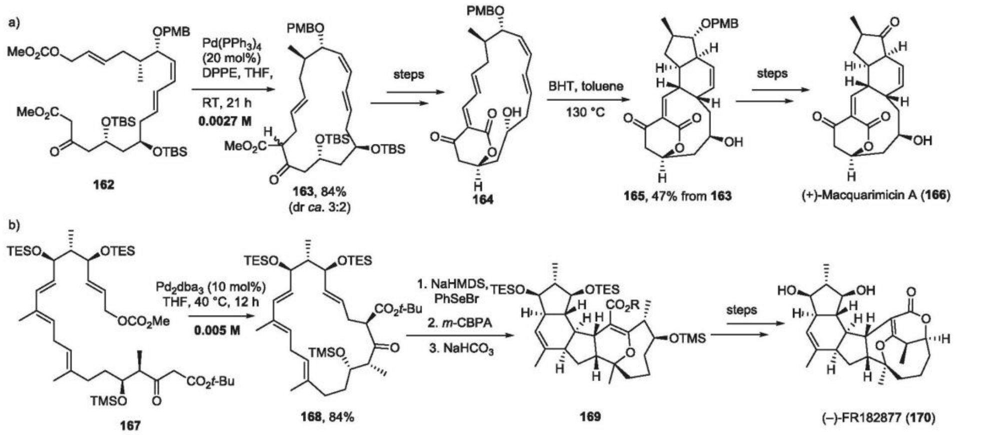
Separately, the groups of Sorensen and Tadano have reported the syntheses of the related polyketide-derived natural products (+)-macquarimicins A–C[144,146] and (−)-FR182877 (**170**)[145] using an innovative transannular Diels–Alder reaction, preceded by a Tsuji–Trost macrocyclisation reaction (Scheme 43). Both used a β-ketoester to react with an allylic carbonate and were able to effect the required cyclisation in impressive yield. Subsequent transannular Diels–Alder reactions proceeded smoothly in both cases to afford the natural product framework. In the case of (−)-FR182877, the team was able to synthesise multigram quantities (5.4 g) of the



Scheme 42. Tsuji–Trost reaction between a silyl enol ether and an allylic carbonate to effect macrocyclisation in the total synthesis of δ-araneosene (Corey and Hu, 2002)[142] (DPPF=1,1′-bis(diphenylphosphino)ferrocene).



Scheme 44. Silicon-assisted palladium-catalysed macrocyclisation reaction used in model studies of oximidine II (Denmark et al., 2010).[151]



Scheme 43. Examples of an intramolecular Tsuji–Trost reaction followed by transannular Diels–Alder reaction in the total synthesis of a) (+)-macquarimicin A (Tadano et al., 2003)[144] and b) (−)-FR182877 (Sorensen et al., 2002)[145] (BHT=3,5-di-*tert*-butyl-4-hydroxytoluene).

direct precursor (the natural product is known to be unstable) using this route. It also allowed correction of the reported structure to the natural enantiomer.[147]

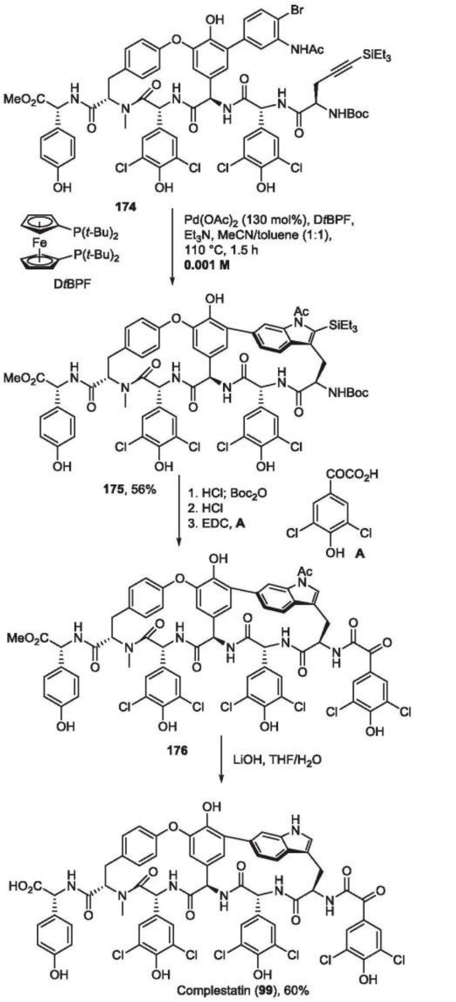
8. Miscellaneous reactions

There are a number of original and inventive palladium-catalysed macrocyclisation methods which have been employed in natural product total synthesis but which fall outside the classifications of traditional cross-coupling reactions.

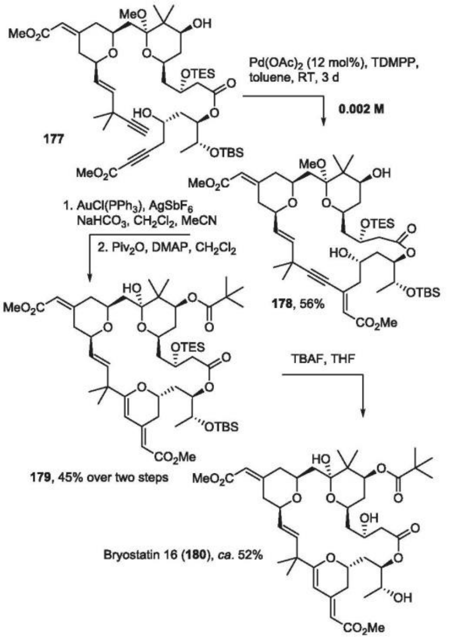
Denmark and co-workers have reported an innovative silicon-assisted palladium-catalysed cross-coupling reaction. Originally developed for medium-ring compounds,[148] its synthetic utility was showcased in the total synthesis of nine-membered cyclic ether (+)-brasilenyne.[149,150] It was subsequently also demonstrated to be an effective method for the synthesis of polyunsaturated macrolactones as shown in the context of a model system for the 12-membered macrocycle oximidine II (**86**, Scheme 44).[151] The method involves the silicon-assisted cross-coupling reaction of an unsaturated siloxane ring with an alkenyl iodide (**172**). The cycloalkenylsiloxanes are readily available via ring-closing metathesis chemistry from precursors such as **171**. After an extensive optimisation, $[Pd(allyl)Cl]_2$ and TBAF·$6H_2O$ in DMF provided the desired macrocycle (**173**) in 74% yield.

Boger and co-workers have employed a Larock indole synthesis as a macrocyclisation step in the total synthesis of complestatin (**99**) (chloropeptin II) and its subsequent conversion into chloropeptin I (**57**) (Scheme 45).[152,153] They later adapted this approach as a general method for the formation of indole-containing macrocycles.[154] The Larock indole synthesis, initially reported using iodoanilines[155,156] and subsequently developed by Farina and Senanayake to allow the use of bromo- and chloroanilines,[157] involves the palladium-catalysed reaction between a 2-halo-aniline and an internal alkyne; this work represents the first use of the Larock indole procedure as a macrocyclisation step. Optimisation of the reported procedure for macrocyclisation identified the ideal conditions as using $Pd(OAc)_2$, 1,1′-bis(di-*tert*-butylphosphino)ferrocene (D*t*BPF), Et_3N in toluene/MeCN (1:1) at 110 °C, and they found that this cyclisation could be employed at a late stage in the synthesis with complete atropodiastereoselectivity and good yield. This result represented an improvement on their first generation synthesis when this step was carried out earlier, before the installation of the first ring, and gave only 4:1 *R*:*S*, albeit in higher yield.

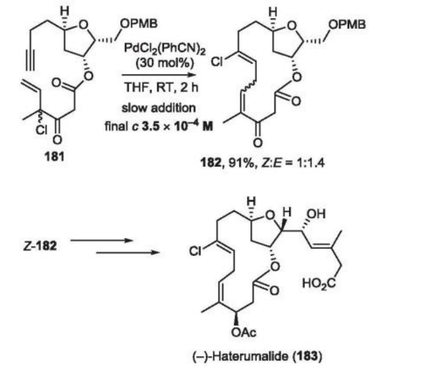
Trost and Dong have reported an interesting palladium-catalysed macrocyclisation in their total synthesis of bryostatin 16 (**180**), a 20-membered macrocycle isolated from the marine bryozoan *Bugula neritina* (Scheme 46).[158,159] Originally reported by Trost



Scheme 45. Use of the Larock indole synthesis as a macrocyclisation step in the total synthesis of complestatin (Boger et al., 2009).[152]



Scheme 46. Unusual cycloisomerisation reaction used in the total synthesis of bryostatin 16 (Trost and Dong, 2008)[158] (TDMPP=tris(2,6-dimethoxyphenyl) phosphine).

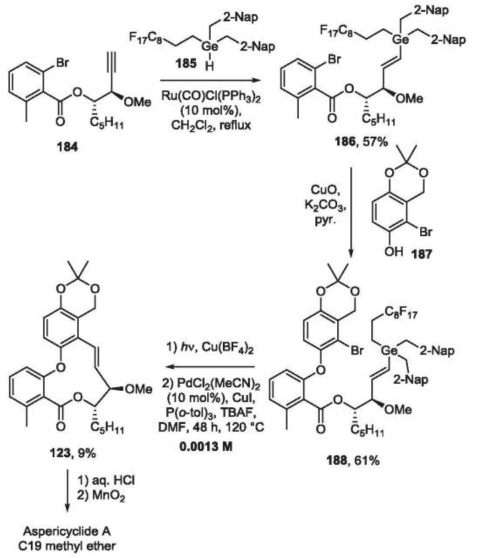


Scheme 47. Pd-catalysed allylation used as a macrocyclisation step in the total synthesis of (−)-haterumalide (Wang et al., 2005).[161]

in 1989,[160] this example represents the first use of this reaction in natural product total synthesis. The efficient process is a cycloisomerisation reaction between a terminal and internal alkyne to form an enyne; this can subsequently react further to form a diene. In the case of bryostatin, the cyclisation proceeds efficiently with precursor **177** to form the macrocycle (**178**) in 56% yield. The resulting internal alkyne then undergoes a second, gold-catalysed cyclisation to form a dihydropyran (**179**); global deprotection affords the target compound.

In their 2005 total synthesis of the cytotoxic, 14-membered macrolactone (−)-haterumalide NA (**183**, also known as (−)-oocydin A),[161] Hoye and Wang applied an infrequently used Pd-catalysed allylation reaction, originally developed by Kaneda and co-workers,[162] to effect a macrocyclisation (Scheme 47). They were able to react a tertiary allylic chloride intramolecularly with a terminal alkyne in the presence of $PdCl_2(PhCN)_2$ to afford the desired macrocycle (**182**) smoothly in 91% overall yield and a 1:1.4 *Z*:*E* ratio across the $\Delta^{4,5}$-alkene.

Spivey and co-workers reported an intriguing modification of the Stille reaction in their total synthesis of the methyl ether of aspercyclide A, a natural product they have previously synthesised using an intramolecular Heck reaction[115] (Scheme 48). They employed a germanium-based coupling partner for their macrocyclisation step, citing the reduced toxicity of germanium compared to tin residues and presumed greater stability to basic and



Scheme 48. Macrocyclisation via a germyl-Stille reaction in the total synthesis of aspercyclide A (Spivey et al., 2011)[163] (Nap=naphthyl).

nucleophilic conditions.[163] The germyl group could be introduced in a Ru-catalysed hydrogermylation reaction with alkyne **185**; a biaryl ether coupling with phenol **187** then gave the cyclisation precursor (**188**). The low polarity of the Ge–C bond requires that the germyl group be activated prior to cross coupling, and this was achieved using $Cu(BF_4)_2$ and photo-activation, a protocol developed previously within the group.[164,165] The resulting product was used immediately in the intramolecular Pd-catalysed cross-coupling to give the desired macrocycle in 9% yield along with a considerable amount (20%) of degermylated side-product.

9. Conclusion

This review has collated a diverse array of Pd-catalysed reactions, which have been exemplified in the total syntheses of some challenging macrocyclic natural products. Macrocycles can be formed in a mild and efficient manner in both complex and multifunctional systems showcasing Pd-based chemistry as a key reaction class for total synthesis. Moreover, we believe there is much potential in the utilisation of Pd-catalysed reactions in the synthesis of other types of macrocyclic compounds, which is a relatively unexplored area with great potential.

Despite this success, there remain challenges to be met. These include increasing the atom economy of these reactions and reducing the high metal catalyst loadings used, a drawback suffered by many of the reactions discussed above. Heck macrocyclisations in particular are frequently not even catalytic, using greater than one equivalent of palladium(II) salts (which need to be reduced to palladium(0) by base or alternative reagent). Whilst in these situations the value of the organic intermediates and final target compounds is considerably higher than the amount of precious palladium catalyst used, there is an argument that can be made that greater elemental sustainability is required concerning the total amount of palladium used. Also, at the present time the raw price of palladium is four times greater than it was in 2008; the value of this precious metal continues to fluctuate, reaching an all-time high in 2000 and relative all-time low in 2008.

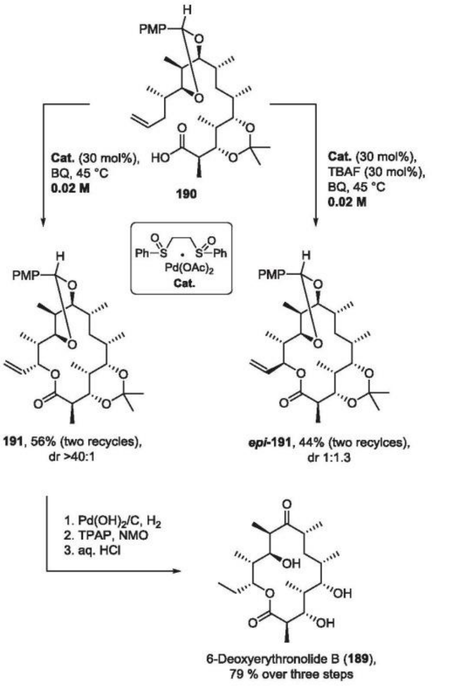
Fully utilising the wide array of catalysts available for different coupling reactions is another challenge for palladium-catalysed reactions, especially in the context of total synthesis. Of the more than 160 individual palladium catalysts currently available commercially (Sigma-Aldrich), only 13 have been employed in the reactions discussed in this review, representing around 8% of the total. Many more catalysts are reported in the literature. This illustrates that Pd catalysis has a huge amount of untapped potential beyond the current preponderance of five or so classes of coupling reaction. For example, palladium-catalysed direct C–H functionalisation, a reaction class with huge potential for natural product total synthesis, has yet to have a serious impact on the field. As the final paragraph in this review demonstrates, if new and innovative reactions can be developed, this will undoubtedly allow access to novel scaffolds and thence to ever more complex targets. The design and synthesis of novel palladium catalysts, or precatalysts, will certainly play a role in the development of milder, more efficient and more selective palladium-catalysed macrocyclisation processes.

One could consider the use of palladium nanoparticles,[166,167] which are highly active catalysts for a raft of traditional cross-coupling reactions, in natural product total synthesis. The synthetic chemistry community has yet to embrace the use of Pd nanoparticles as catalysts, but they arguably offer considerable potential. Similarly, other supported Pd catalysts such as Pd/C exhibit activity, which is complementary to $Pd(OAc)_2$. A rare example of the use of a supported Pd catalyst was shown in Scheme 3 earlier. In some C–H bond functionalisation chemistry, Pd/C can alter the regioselectivity observed in benzothiophene arylation.[168] Pd nanoparticles stabilised by the polymer polyvinylpyrrolidinone (PVP) also show catalytic activity commensurate[169–171] with $Pd(OAc)_2$, and in certain cases activity which exceeds that of $Pd(OAc)_2$.[166,172]

The synthetic community should also be alerted to the complex behaviour of the Pd_2dba_3 catalyst, which is the most commonly employed phosphine-free source of palladium(0). A large number of groups commonly refer to this complex as $Pd(dba)_2$, and whilst this Pd/dba ratio is correct, in solution the complex present is actually $Pd_2dba_3 \cdot dba$.[173] In recrystallised form this complex exists as $Pd_2dba_3 \cdot$solvent (where solvent=$CHCl_3$, CH_2Cl_2, toluene, benzene etc.).[173] The presence of Pd nanoparticles, formed in the preparation of Pd_2dba_3 complexes and on standing in solution, could also influence cross-coupling efficacy, either positively or negatively.[174]

In an exciting demonstration of the future potential of Pd-catalysed macrocyclisations in the field of total synthesis, White and co-workers have recently employed late-stage oxidative C–H functionalisation in their total synthesis of 6-deoxyerythronolide B (**189**, Scheme 49).[175,176] In a remarkable display of selectivity, they were able to cyclise their precursor **190** to form a single diastereomer of the macrolide **191** in 56% yield after two recycles, using reaction conditions previously developed by them.[175] Compound **191** could be straightforwardly converted into the target compound **189** in three steps. Furthermore, they found that by disrupting the chelation control in the macrocyclisation step using a fluoride source, they could reverse the selectivity to obtain the unnatural epimer of their cyclisation product, ***epi*-191**, in 44% yield. The cyclisation of the natural epimer (but not the unnatural one) could also be achieved using an intermolecular C–H oxidation followed by a Yamaguchi macrolactonisation.

White's approach shows how innovative C–H bond activation chemistry can be used in complex target-oriented synthesis with great effect. It is an approach that holds much promise for the future.



Scheme 49. First use of Pd-catalysed C–H oxidation as a macrocyclisation strategy in the total synthesis of 6-deoxyerythronolide B (White et al. 2009).[176]

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AsCat and FurCat: new Pd catalysts for selective room-temperature Stille cross-couplings of benzyl chlorides with organostannanes†

Thomas O. Ronson, Jonathan R. Carney, Adrian C. Whitwood, Richard J. K. Taylor and Ian J. S. Fairlamb*

Two novel succinimide-based palladium complexes, AsCat and FurCat, are highly efficient catalysts for room-temperature Stille cross-coupling of organostannanes with benzyl chlorides. The air- and moisture-stable catalysts are prepared in one step, and the coupling reactions proceed with a high selectivity for the benzyl position under mild conditions without the need for additives.

The Pd-catalysed cross-coupling reaction between organostannanes and halides or pseudohalide electrophiles, known as the Stille cross-coupling (SCC) reaction,[1] finds widespread use in the synthesis of complex organic molecules.[2] Its inherent mildness and functional group compatibility are borne out by its frequent use at a late stage in the total synthesis of complex natural products.[3] Moreover, mechanistic investigations have led to significant developments in the catalytic systems and conditions employed to effect the Stille coupling, permitting ever more efficient reactions.[4]

Diarylmethanes are useful substructures present in many biologically active compounds.[5] Palladium catalysis has emerged as a useful method to access these types of structural units,[6] but despite its potential, the SCC reaction has received relatively little attention in this regard, with only limited reports of couplings between organostannanes and benzyl halides.[7] These typically require the use of elevated temperatures and/or a Lewis basic additive to achieve efficient reaction. Although room-temperature SCC reactions are established with certain electrophiles,[8] less reactive substrates can require specially designed catalyst systems.[9] There have been only sporadic reports of room-temperature SCC reactions between organostannanes and benzyl bromides,[10] and are no dedicated reports with benzylic chlorides. The ability to carry out these transformations mildly on a range of substrates under simple conditions would be of great value to synthetic chemistry.

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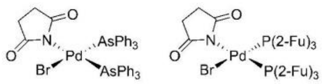
In previous studies, we have shown that Pd catalysts bearing one or more imidate ligands exhibit an unusually high efficiency in Stille and Suzuki–Miyaura cross-couplings involving allylic and benzylic electrophiles.[7b–e,11] Imidate ligands have a number of different coordination modes and similar electronic properties to halide ligands, and are proposed to play a key part in this observed selectivity.

As part of our endeavours to develop new catalysts for SCCs, we proposed that succinimide-containing Pd catalysts incorporating the labile triphenylarsine and tri(2-furyl)phosphine ligands, which have been shown to offer dramatic rate enhancements in Stille couplings,[12] could be efficient new catalysts. We report herein two novel succinimide-containing Pd complexes, Pd(*N*-succ)Br($AsPh_3)_2$ (**1**, AsCat) and Pd(*N*-succ)Br($P(2\text{-}Fu)_3)_2$ (**2**, FurCat) (Fig. 1, depicted with a *cis*-geometry), which are effective catalysts for SCC reactions with benzyl halides at ambient temperature.

Both complexes were synthesised by treating $Pd_2dba_3{\cdot}CHCl_3$ with the appropriate ligand (L, 2 equiv. per Pd) in CH_2Cl_2, followed by oxidative addition of *N*-bromosuccinimide (NBS, 1 equiv. per Pd) (Scheme 1).

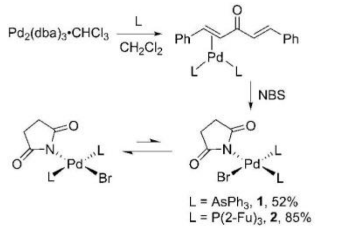
The desired complexes were obtained in moderate-to-high yields as pale brown solids, and although labile in solution, they were found to be air- and moisture-stable in the solid state. Complex **1** exists in a *ca.* 4 : 1 *cis*/*trans*-ratio on isolation (^1H NMR spectroscopy), with complete isomerisation to the *trans*-isomer seen after 24 h at RT in $CDCl_3$ or CD_2Cl_2 solution (Scheme 1). Complex **2** exhibits a similar behaviour, with both the ^1H and ^{31}P NMR spectra indicating an approximately 9:1 *cis*/*trans*-ratio on isolation. Isomerisation is slower in the case of **2** (1 : 1, *cis*/*trans* after 24 h at RT in $CDCl_3$ solution).



1
AsCat

2
FurCat

Fig. 1 Structures of the two novel succinimide-based catalysts, **1** and **2**.



Scheme 1 Synthesis of complexes **1** (AsCat) and **2** (FurCat).

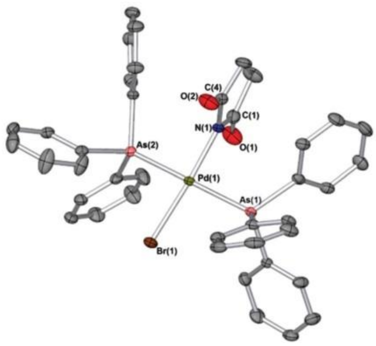
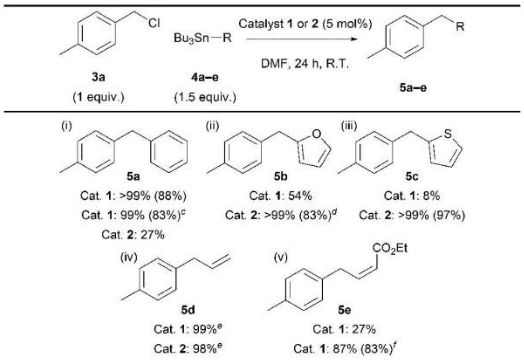


Fig. 2 The crystal structure of complex **1**. Hydrogen atoms have been removed and only selected atoms are numbered for clarity. Thermal ellipsoids are shown with a probability of 50%. Selected bond lengths (Å): Pd(1)–As(1): 2.4229(4), Pd(1)–Br(1): 2.4338(4), Pd(1)–As(2): 2.3914(4), Pd(1)–N(1): 2.025(2). Selected bond angles (°): N(1)–Pd(1)–As(1): 90.69(7), As(1)–Pd(1)–Br(1): 92.969(13), Br(1)–Pd(1)–As(2): 87.471(13).

A single crystal X-ray diffraction structure of *trans*-**1** was obtained (Fig. 2), with the crystals grown by vapour diffusion of pentane into a saturated solution of the complex in CH_2Cl_2.

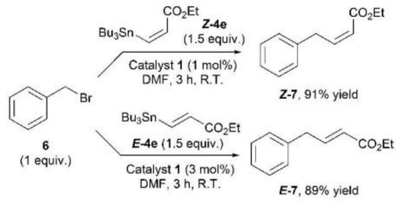
Catalyst screening showed that **1** and **2** are highly active catalysts, being able to mediate the coupling of 4-methylbenzyl chloride (**3a**) with a variety of stannanes in DMF at room temperature (Table 1). Product conversions were dependent on both the catalyst and stannane used, but the catalytic ability of the complexes appears to be complementary. The triphenylarsine-based catalyst **1** was efficient at mediating coupling with tributylphenylstannane **4a** in both DMF and propylene carbonate (entry i, Table 1), whilst the tri(2-furyl)phosphine-based catalyst **2** gave only modest conversion (the analogous triphenylphosphine-based succinimide catalyst, Pd(*N*-succ)Br(PPh_3)$_2$, gave no conversion at room temperature). Conversely, coupling of the electron-rich heteroaromatic stannanes **4b** and **4c**, based on furan and thiophene respectively, was efficiently mediated by complex **2**, but not by **1** (entries ii and iii, Table 1). Both catalysts were efficient with tributylvinylstannane **4d** (entry iv, Table 1). Note that, when required, pure products could be readily obtained following a simple aqueous workup and flash chromatography using SiO_2–K_2CO_3 (9 : 1, w/w) as the stationary phase in order to remove organotin impurities.[13]

Table 1 Stille cross couplings of 4-methylbenzyl chloride **3a** with various stannanes using catalysts **1** and **2**[a,b]



[a] Percentages refer to conversion to product as judged by ^{1}H NMR spectroscopy. [b] Percentages in parentheses refer to yields of isolated product following purification on SiO_2–K_2CO_3. [c] Reaction conducted using propylene carbonate solvent as a substitute for DMF. [d] Reaction time 3 h. [e] Product not isolated due to volatility. [f] Reaction time 72 h.

The electron-deficient stannane ***Z*-4e** could also be coupled using the more reactive catalyst **1**, although a longer reaction time was required for higher product conversions (entry v, Table 1). By contrast, stannanes ***E*-** and ***Z*-4e** could be coupled rapidly with benzyl bromide (**6**) catalysed by complex **1** at lower catalyst loadings and ambient temperature (Scheme 2), affording products ***E*-** and ***Z*-7**.

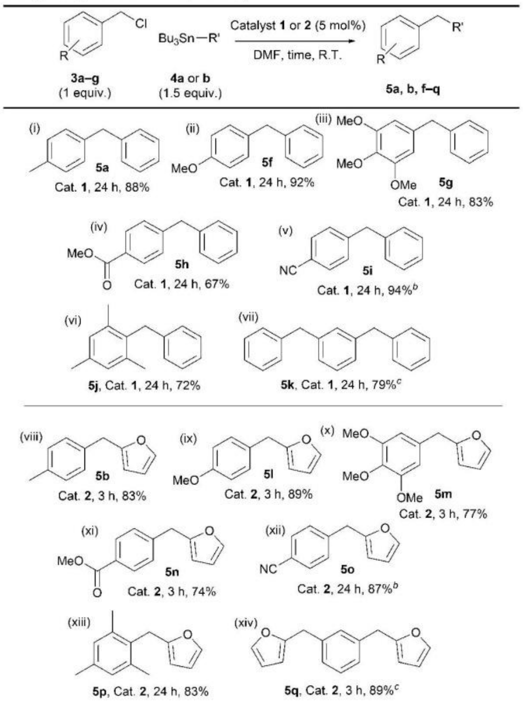


Scheme 2 Coupling of benzyl bromide (**6**) with electron deficient stannanes ***E*-** and ***Z*-4e** using catalyst **1**.

The scope of benzyl chloride coupling partners was explored next (Table 2), and both catalysts are found to be fully compatible with a range of substitution on the aryl group. Electron-rich (entries ii, iii, ix and x, Table 2) and electron-deficient (entries iv and xi, Table 2) substrates were coupled effectively with both catalysts, although very electron-poor benzyl chlorides (entries v and xii, Table 2) required gentle heating for efficient reaction. We interpret this observation as being due to a difference in transmetallation rates of the oxidative addition Pd^{II} intermediates, or a different mechanism to the traditional Pd^0/Pd^{II} catalytic cycle.[4a] Substitution *ortho*- to the benzyl position was also tolerated (entries vi and xiii, Table 2), as was a double coupling on a bis-benzyl chloride (entries vii and xiv, Table 2).

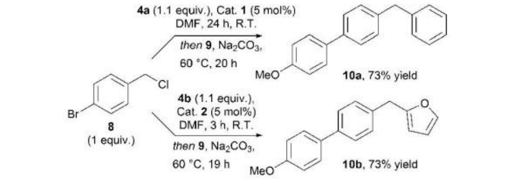
One of the most useful aspects of our new catalysts is the high selectivity which they display for coupling of benzyl electrophiles

Table 2 Coupling of stannanes **4a** and **4b** with various benzyl chlorides **3** using catalysts **1** and **2** respectively[a]



[a] Percentages refer to yields of isolated product following purification on SiO_2–K_2CO_3. [b] Reaction carried out at 40 °C. [c] Reaction carried out with 3 equiv. of stannane and 6 mol% catalyst.

over aryl electrophiles. Selectivity for a benzyl bromide over an aryl bromide has been previously demonstrated with similar complexes,[7c] however, there is no instance in the literature of the SCC with a benzyl chloride in the presence of an aryl bromide. In order to illustrate this selectivity, we carried out the reaction of 4-bromobenzyl chloride (**8**) with stannanes **4a** and **4b** using catalysts **1** and **2** respectively (Scheme 3). The intermediates (not isolated) were subjected to a Suzuki–Miyaura coupling with 4-methoxyphenylboronic acid (**9**), without the further addition of catalyst, and this allowed the isolation of the desired products **10a** and **10b**, both in 73% yield, effectively demonstrating the unusual selectivity of these catalysts.



Scheme 3 Tandem Stille–Suzuki cross-coupling reactions demonstrating the selectivity of both catalysts for the benzyl chloride over an aryl bromide.

In conclusion, two novel catalysts, AsCat (**1**) and FurCat (**2**), exhibit remarkable activity in the first reported examples of room-temperature SCC reactions with benzyl chlorides. Both catalysts show a useful selectivity for benzyl chlorides over aryl bromides, tolerating a range of functionality including electron-deficient and electron-rich benzyl chlorides, and exhibit an intriguing complementarity with respect to the structure of the organostannane. The SCC reactions greatly benefit from being mild, simple and highly efficient; their broader use in the synthesis of complex organic molecules is anticipated. Detailed mechanistic investigations are ongoing and will be reported in due course.

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Macrocyclic polyenynes: a stereoselective route to vinyl-ether-containing skipped diene systems†‡

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The stereoselective synthesis of a challenging macrocyclic polyene scaffold, containing a sensitive vinyl ether motif, has been accomplished using *O,C*-dilithiation/selective *C*-alkylation, Pd-catalysed etherification and Wittig reactions as key steps. An end-game macrocyclisation strategy employed a regio- and stereoselective Stille cross-coupling using $Pd(Br)(N\text{-}Succ)(AsPh_3)_2$ (AsCat) as the precatalyst.

Skipped diene (1,4-diene) motifs are synthetically valuable subcomponents found in an eclectic array of bioactive natural products. Examples include macrocyclic compounds such as phacelocarpus 2-pyrone A,[1] labillaride C,[2] ripostatin B[3] and neurymenolide A[4] (Fig. 1). These chemical structures provide a stiff examination of any synthetic methodology that facilitates the construction of isolated or multiply bonded 1,4-diene systems embedded within these types of macrocycles.[5] For ripostatin B two synthetic approaches to the 1,4-diene motif were simultaneously reported by Christmann[6] and Prusov[7] employing alkene metathesis. Fürstner[8] employed alkyne metathesis, and a variety of organometallic cross-coupling methods, to access the 1,4-dienes embedded within neurymenolide A, where he also applied an Au-catalysed process to reveal the core 2-pyrone motif. Related to the ripostatin family, Sigman developed a Pd-catalysed 1,4-vinylvinylation methodology using 1,3-butadiene, vinyl triflates and vinyl boronates.[9] Despite these successes there are still many challenges associated with the selective synthesis of 1,4-diene containing products.

Macrocycle **1** (Scheme 1) is a structural mimetic of phacelocarpus 2-pyrone A, a target in which we have been interested for some time.[10] Only one model study towards this natural

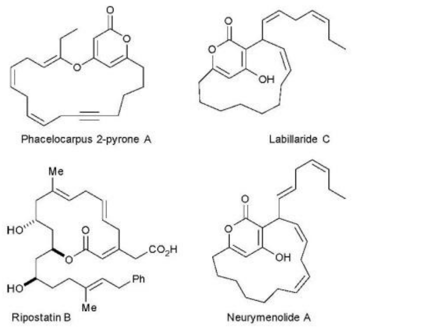
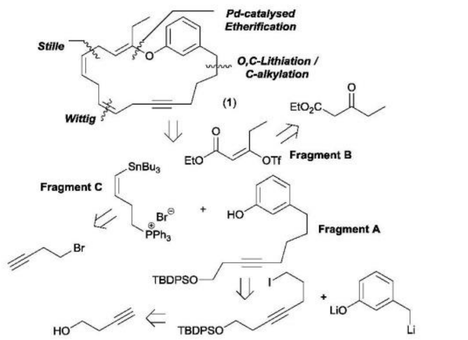


Fig. 1 Exemplar macrocyclic natural products containing 1,4-diene motifs.



Scheme 1 Proposed retrosynthetic analysis of macrocyclic target compound **1**.

product, exploring a ring-closing alkyne metathesis route, has previously been carried out.[11] We wished to synthesise **1** for the following reasons: (a) it contains four skipped centres of unsaturation (two with *Z*-stereochemistry) and a novel embedded skipped 1,4-diene motif containing an (*E*)-vinyl ether; (b) formation

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† Abbreviations: XPhos, (2-dicyclohexylphosphino-2′,4′,6′-triisopropyl biphenyl); DMP, Dess–Martin perodinane; DIBAL-H, diisobutylaluminium hydride; TBAF, tetra-*n*-butyl ammonium fluoride; DMAP, dimethyl aminopyridine; TBDPS, *tert*-butyldiphenylsilyl; TMEDA, tetramethylethyldiamine.

‡ Electronic supplementary information (ESI) available: Experimental and full characterisation details. See DOI: 10.1039/c5cc02091c

of a polyene/yne macrocyclic structure, using Stille cross-coupling in the final step, was particularly appealing as we have previously developed catalysts for this purpose;[10c,d] (c) an arene mimetic could increase the intrinsic stability of the macrocycle, allowing new synthetic analogues to be identified for drug discovery.[10e]

A retrosynthetic analysis to macrocycle **1** is shown in Scheme 1. We identified four key disconnections, revealing three synthetic fragments A–C. We recognised that the non-trivial trisubstituted vinyl ether could be accessed by a Pd-catalysed etherification reaction, allowing fragments A and B to be connected.[12] The synthesis of the fragment A could be achieved by selective *C*-alkylation of the dilithium salt derived from *m*-cresol.[13] The adventurous branch within the retrosynthetic route exploits the dual nucleophilic reactivity of (*Z*)-1-tributylstannyl-but-1-en-4-triphenylphosphonium bromide (the key vinylstannyl–phosphonium salt, fragment C), allowing sequential Wittig reaction[14] and Stille cross-coupling[15] to be assessed, along with any associated regio- and stereoselectivity. We postulated that the Stille cross-coupling was best suited to the last step, to deliver the macrocyclic target compound **1**.[16]

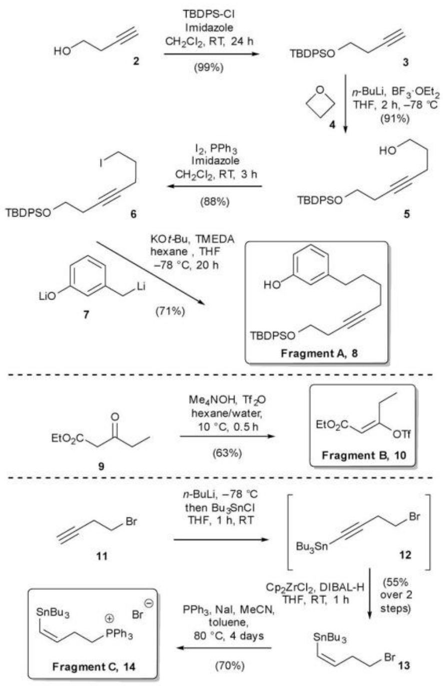
The forward synthetic route began with the synthesis of fragments A–C (Scheme 2). Fragment A was prepared from the homopropargylic alcohol **2**, by silyl protection to give **3**, then alkylation of the terminal alkyne with oxetane **4**, giving **5** in high yield. Iodination to give **6**, and then subsequent alkylation of the dilithium salt of *m*-cresol **7** with the primary iodide, gave compound **8** (fragment A) in good overall yield.

Fragment B was efficiently prepared using Frantz's method,[17] by reaction of commercially available β-ketoester **9** with Me_4NOH and Tf_2O, giving (*E*)-enol triflate **10** (fragment B) selectively in 63% yield.

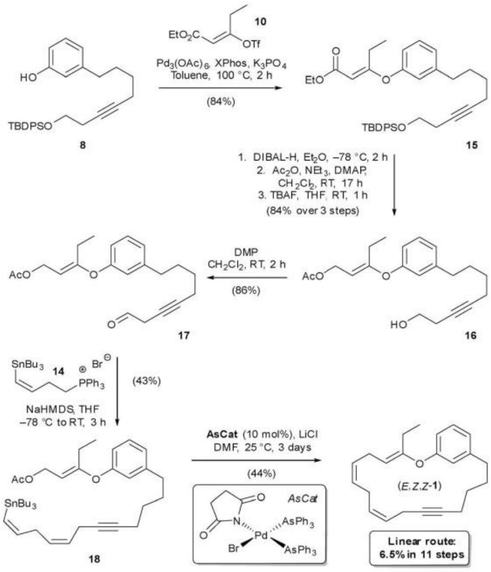
Fragment C was synthesised starting from homopropargylic bromide **11**, which was lithiated on the terminal alkyne and then trapped with *n*-Bu_3SnCl to give alkynyl stannane **12** in good yield. The synthesis of (*Z*)-stannane **13** was accomplished using *in situ* generated Schwartz reagent, $Cp_2Zr(H)Cl$,[18] giving **13** which was reacted directly with PPh_3 to give phosphonium salt **14** (fragment C) in good yield.

The end-game synthetic route is described in Scheme 3. Phenolic compound **8** (fragment A) was subjected to a highly novel Buchwald–Hartwig type etherification[12] by reaction with (*E*)-enol triflate **10**, mediated by a precatalyst consisting of $Pd_3(OAc)_6$ (>99% purity) and the XPhos ligand (Pd : XPhos = 1 : 2), which gave (*E*)-enol ether product **15** in 84% yield. The vinyl ester functionality within **15** was then reduced to the alcohol with DIBAL-H and acetylated under standard conditions. Subsequent silyl deprotection with TBAF afforded compound **16** in 84% yield (over 3 steps). A mild and neutral protocol for the Dess–Martin perodinane (DMP) oxidation[19] of **16** afforded aldehyde **17** in 86% yield.

The final sequence for the synthetic route involved reaction of Wittig reagent **14** (fragment C) with aldehyde **17** to give **18** in 43% yield.[20,21] Only the *Z* stereoisomer was formed, and the (*Z*)-vinyl stannane was also retained. The last step unites the (*Z*)-vinyl stannane and allylic vinyl ether components. The allylic



Scheme 2 Synthesis of fragments A–C.



Scheme 3 End-game synthesis of macrocycle **1**.

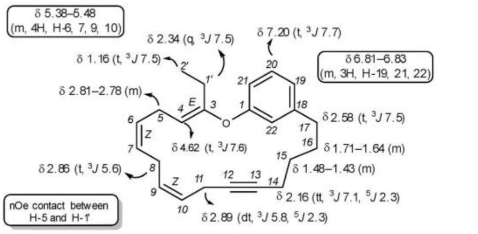


Fig. 2 Key ^{1}H NMR spectroscopic data for (*E*,*Z*,*Z*)-**1** (major stereoisomer).

centre creates the potential for S_N2 and S_N2' products being formed from $Pd^{II}(\pi\text{-allyl})(OAc)L_n$ or $Pd^{II}(\pi\text{-allyl})(R)L_n$ intermediates; any π–σ–π equilibration could influence the alkene stereochemistry. The Stille cross-coupling macrocyclisation reaction was run at low concentration (0.02 M). We initially evaluated the established and widely used catalyst system $Pd_2(dba)_3{\cdot}CHCl_3$/$AsPh_3$ (Pd : $AsPh_3$ = 1 : 2),[22] which gave the target compound **1** in 28% yield (isolated product).

Whilst the preliminary result encouraged us, we were pleased to establish that our in-house developed precatalyst for Stille cross-couplings of benzyl halides with organostannanes,[23] $Pd(Br)(N\text{-Succ})(AsPh_3)_2$ ('AsCat'), worked well for this particular macrocyclisation Stille cross-coupling, affording **1** in 44% yield (*E* : *Z* ratio = 5 : 1 about the vinyl ether bond, determined by ^{1}H NMR spectroscopy) after preparatory thin layer chromatography.

The structural connectivity of **1** was confirmed by NMR spectroscopic analysis. The ^{1}H NMR data is collated in Fig. 2 (complete ^{1}H/^{13}C correlations are collated in the ESI‡). The location of the methylene protons (H-1′) allowed us to track the connectivity through to H-5. A clear nOe contact between H-1′ and H-5 was observed by a NOESY experiment, confirming the stereochemistry of the vinyl ether as *E* in the major isomer.

In summary, we have described the stereoselective synthesis of a challenging macrocyclic polyene scaffold **1**, containing a sensitive vinyl ether motif. A series of key steps, namely selective *O*,*C*-dilithiation/*C*-alkylation, Pd-catalysed etherification, Wittig and Stille cross-coupling reactions were needed to ensure success. A highlight of the synthetic route is the first use of a vinyl stannane containing an alkyl phosphonium bromide,[21] where its intrinsic dual nucleophilic character has been used in sequential Wittig and Stille cross-coupling reactions. The utility of $Pd(Br)(N\text{-Succ})(AsPh_3)_2$, 'AsCat', as a Stille cross-coupling precatalyst,[23] has been demonstrated, holding much promise for its wider application in cross-coupling catalysis and target-orientated synthesis.[16]

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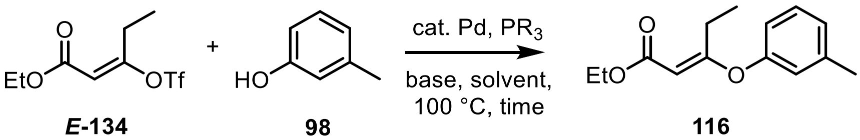
Appendix 2: Tables of Reaction Data

Table 22 Optimisation of Pd-catalysed etherification reaction (Chapter 2).

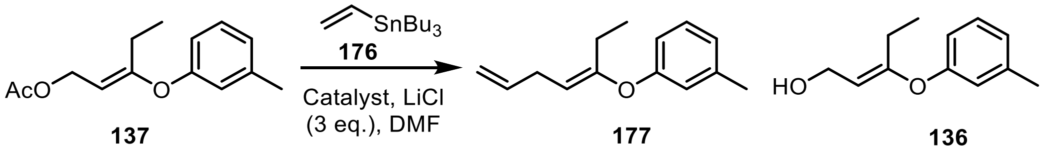


Entry	Catalyst [mol%]	Ligand [mol%]	Base [eq.]	Solvent	Time / h	Yield / %[a]
1	$Pd(OAc)_2$ [2]	Q-Phos [3]	K_3PO_4 [2]	toluene	24	48
2	$Pd(OAc)_2$ [5]	Q-Phos [5]	K_3PO_4 [2]	toluene	24	56
3	$Pd(OAc)_2$ [5]	Q-Phos [5]	K_3PO_4 [2]	toluene	24	31[b]
4	$Pd(OAc)_2$ [5]	X-Phos [5]	K_3PO_4 [2]	toluene	24	75
5	$Pd(OAc)_2$ [2.5]	X-Phos [5]	K_3PO_4 [2]	toluene	2	75
6	$Pd(OAc)_2$ [2.5]	X-Phos [5]	K_3PO_4 [2]	DMF	2	61
7	$Pd(OAc)_2$ [5]	JohnPhos [5]	K_3PO_4 [2]	toluene	24	38
8	$Pd_2(dba)_3$ [3]	JohnPhos [9]	*t*-BuONa [1.5]	toluene	24	19
9	*cis*-**23** [5]	-	K_3PO_4 [2]	toluene	24	47
10	*cis*-**23** [5]	$PCy_3{\cdot}HBF_4$ [10]	K_3PO_4 [2]	toluene	24	23
11	*trans*-**23** [2.5]	X-Phos [5]	K_3PO_4 [2]	DMF	2	60
12	*trans*-**23** [2.5]	X-Phos [5]	Cs_2CO_3 [2]	DMF	2	50
13	*trans*-**23** [2.5]	-	K_2CO_3 [2]	DMF	1	-[c]
14	*trans*-**23** [2.5]	-	*t*-BuONa [2]	DMF	1	-[d]
15	*trans*-**23** [2.5]	-	2,6-lutidine [2]	DMF	24	-[d]
16	*trans*-**23** [2.5]	-	K_3PO_4 [2]	DMF	1.5	55
17	*trans*-**23** [2.5]	-	K_3PO_4 [2]	DMF	1.5	50[e]
18	*trans*-**23** [2.5]	-	K_3PO_4 [2]	DMF	1	53[f]
19	*trans*-**23** [2.5]	-	-	DMF	24	-[g]
20	PdNPs [2.5]	X-Phos [5]	K_3PO_4 [2]	DMF	1	44
21	**280** [2.5]	-	K_3PO_4 [2]	DMF	0.3	57
22	**280** [2.5]	X-Phos [5]	K_3PO_4 [2]	DMF	0.3	-[d]

23	**280** [2.5]	-	K_3PO_4 [2]	DMF	1	-[d,h]
24	**229** [2.5]	-	K_3PO_4 [2]	DMF	0.2	37
25	*trans*-**23** [2.5]	-	K_3PO_4 [2]	DMA	0.7	55
26	$Pd(OAc)_2$ [2.5]	$P(2\text{-}Fu)_3$ [5]	K_3PO_4 [2]	toluene	1.5	-[d]
27	-	-	K_3PO_4 [2]	toluene	1.5	-[c]

[a]Yield of isolated product after column chromatography. [b]TBAB additive used. [c]Isomerisation of product observed in crude reaction mixture by ^1H NMR spectroscopy. [d]Decomposition observed by ^1H NMR spectroscopy. [e]Reaction exposed to air for 5 s at start of reaction. [f]Reaction carried out at 120 °C. [g]No reaction. [h]Reaction conducted at 50 °C.

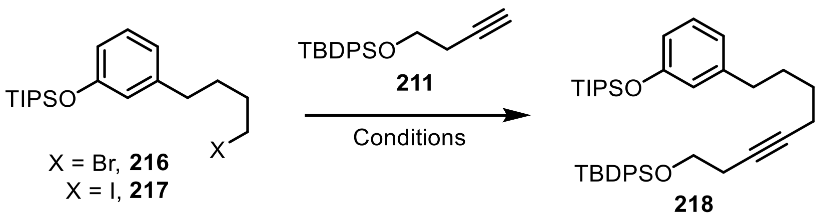
Table 23 Optimisation of allylic Stille reaction (Chapter 2).



Entry	Catalyst [mol%]	Oxidant [eq.]	Ratio **137**:**177**:**136**[a]
1	$Pd_2dba_3{\cdot}dba$ [3]	-	34:58:7
2	$Pd_2dba_3{\cdot}dba$ [3][b]	-	48:35:17
3	$Pd_2dba_3{\cdot}dba$ [3][c]	-	36:53:11
4	$Pd_2dba_3{\cdot}dba$ [6]	-	49:49:2
5	$Pd_2dba_3{\cdot}dba$ [6][b, c]	-	24:62:14
6	$Pd_2dba_3{\cdot}dba$ [3][d]	-	44:42:14
7	$Pd_2dba_3{\cdot}dba$ [3][e]	-	83:17:0
8	$Pd_2dba_3{\cdot}CHCl_3$ [3][c]	-	31:65:4
9	*cis*-**23** [3]	-	92:8:0
10	*trans*-**23** [3]	-	89:11:0
11	*cis*-**23** [3]	air [5 s]	0:80:20
12	*trans*-**23** [3]	air [5 s]	0:80:20
13	*cis*-**23** [3]	air [20 s]	23:55:22
14	*trans*-**23** [3]	air [20 s]	13:66:21
15	*trans*-**23** [3]	$NaBO_3{\cdot}4H_2O$ [0.1]	76:24:0
16	*trans*-**23** [3]	NMO [0.2]	90:10:0
17	Pd(dppf)(*N*-succ)Br [3]	-	100:0:0
18	ABCat [1.5]	-	83:17:0
19	ABCat [1.5]	air [5 s]	75:7:19
20	$PdCl_2(MeCN)_2$ [3]	-	59:32:8
21	*trans*-**23** [3][f]	-	52:48[g]:0
22	*trans*-**23** [3][h]	-	0:100[i]:0

[a]As determined by ^1H NMR spectroscopy. [b]Reaction time 48 h. [c]6 equiv. LiCl used. [d]Reaction conducted at 50 °C. [e]TBAC (1 equiv.) used in place of LiCl. [f]Reaction carried out at 40 °C. [g]*E*:*Z* = 3:1. [h]Reaction carried out at 60 °C. [i]*E*:*Z* = 2:1.

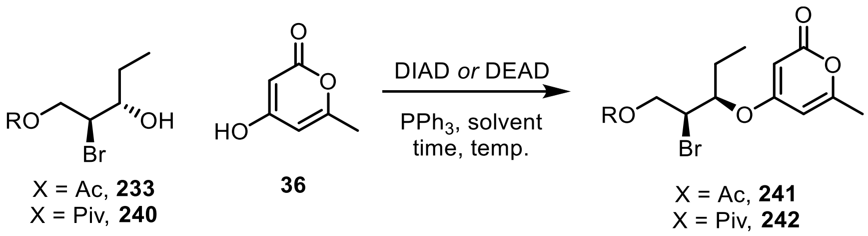
Table 24 Alkylation attempts of terminal alkyne **211** (Chapter 2).



Entry	**X**	**Conditions**	**Temp. / °C**	**Result**[a]
1	Br	*n*-BuLi (1.1 eq.), THF	−78 → 50	no reaction
2	Br	*n*-BuLi (1.1 eq.), HMPA (1.1 eq.), THF	−78 → 50	no product formed
3	Br	*n*-BuLi (1.5 eq.), HMPA (1 eq.), THF	−78 → 50	trace
4	I	*n*-BuLi (1.2 eq.), THF	−78 → 67	no reaction
5	I	*n*-BuLi (1.2 eq.), HMPA (1.1 eq.), THF	−78 → RT	trace
6	I	*n*-BuLi (1.2 eq.), HMPA (1.2 eq.), Et_2O	−78 → 36	no reaction
7	I	*n*-BuLi (1.2 eq.), HMPA (1.2 eq.), hexane	−78 → 70	no reaction
8	I	*n*-BuLi (1.2 eq.), dioxane	−78 → 100	no reaction
9	I	NaHMDS (1.2 eq.), THF	0	no reaction
10	I	*n*-BuLi (1.2 eq.), HMPA (2.4 eq.), THF	−78 → 67	20%[b]
11	I	*n*-BuLi (1.2 eq.), HMPA (5 eq.), THF	−78 → 67	7%[b]
12	I	$[Pd(allyl)Cl]_2$, IPr.HCl, (4-MeO)-dba, CuI, Cs_2CO_3, DMF/Et_2O	40	13%[b]
13	I	Pd_2(4-MeO-dba)$_3$, IPr.HCl, CuI, Cs_2CO_3, DMF/Et_2O	40	7%[b]
14	I	Pd_2(4-MeO-dba)$_3$, IPr.HCl, CuI, Cs_2CO_3, DMF/Et_2O	50	low conversion
15	I	Pd_2(4-MeO-dba)$_3$, IAd.HCl, CuI, Cs_2CO_3, DMF/Et_2O	40	low conversion

[a]As judged by ^{1}H NMR spectroscopy. [b]Yield of isolated product following column chromatrography.

Table 25 Screening of conditions for Mitsunobu reaction of pyrone **36** (Chapter 3).

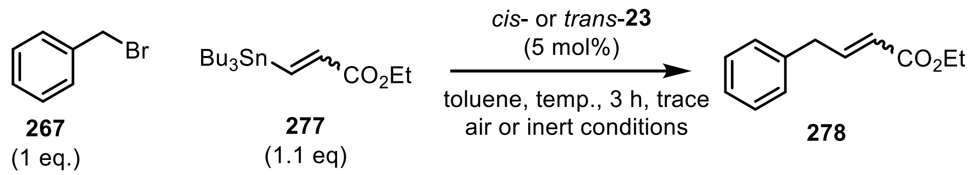


Entry	Reagents	R	Time / h	Solvent	Temp. / °C	Conv. / % [a, b]
1	DIAD (1.2 eq.), PPh_3 (1.2 eq.)	Ac (1.1 eq.)	15	CH_2Cl_2	RT	0
2	DIAD (1.5 eq.), PPh_3 (1.5 eq.)	Ac (1.5 eq.)	6	CH_2Cl_2	RT	0
3	DIAD (1.2 eq.), PPh_3 (1.2 eq.)	Ac (1.1 eq.)	22	CH_2Cl_2	40	42
4	DIAD (2 eq.), PPh_3 (2 eq.)	Ac (1.1 eq.)	24	CH_2Cl_2	40	33
5	DIAD (1.2 eq.), PPh_3 (1.2 eq.)	Ac (1.1 eq.)	23	THF	50	0
6	DIAD (1.2 eq.), PPh_3 (1.2 eq.)	Ac (1.1 eq.)	19	DMF	40	0
7	DIAD (1.5 eq.), PPh_3 (1.5 eq.)	Ac (1.5 eq.)	24	CH_2Cl_2	40	50
8	DIAD (1.5 eq.), PPh_3 (1.5 eq.)	Ac (1.5 eq.)	24	toluene	40	62
9	DEAD (1.5 eq.), PPh_3 (1.5 eq.)	Ac (1.5 eq.)	44	toluene	RT	61
10	DEAD (2 eq.), PPh_3 (2 eq.)	Ac (2 eq.)	21	toluene	RT	100
11	DEAD (0.9 eq.), PPh_3 (0.9 eq.)	Ac (0.9 eq.)	23	toluene	RT	30
12	DEAD (1.7 eq.), PPh_3 (1.7 eq.)	Ac (1.7 eq.)	23	toluene	RT	60
13	DEAD (2 eq.), PPh_3 (2.2 eq.)	Ac (2 eq.)	28	toluene	RT	30
14	DEAD (1.9 eq.), PPh_3 (2 eq.)	Ac (2 eq.)	24	toluene	RT	58
15	DEAD (1.9 eq.), PPh_3 (2 eq.)	Ac (2 eq.)	24	1:1, CH_2Cl_2/tol	RT	37

16	DEAD (1.9 eq.), PPh_3 (2 eq.)	Ac (2 eq.)	24	toluene	40	53 (45)
17	DEAD (2.2 eq.), PPh_3 (2 eq.)	Ac (2 eq.)	23	toluene	RT	56
18	DEAD (1.1 eq.), PPh_3 (1.1 eq.), NeopOH (0.5 eq.)	Ac (1.1 eq.)	24	toluene	RT	0
19	DEAD (1.1 eq.), PPh_3 (1.1 eq.), NeopOH (0.5 eq.)	Ac (1.1 eq.)	24	toluene	40	0
20	DMEAD (1.2 eq.), PPh_3 (1.2 eq.)	Ac (1.2 eq.)	24	toluene	RT	50
21	DEAD (1.5 eq.), PPh_3 (1.5 eq.)	Piv (1.5 eq.)	23	toluene	RT	32
22	DEAD (2 eq.), PPh_3 (2 eq.)	Piv (2 eq.)	25	toluene	–78 to RT	69 (66)

[a]As judged by ^{1}H NMR spectroscopy. [b]Yields of isolated product in parentheses.

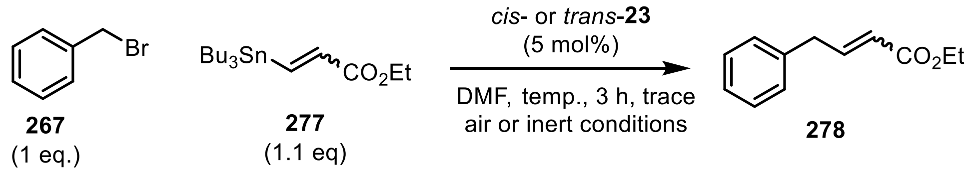
Table 26 Data for reactions Stille reactions using catalyst **23** carried out in toluene (Chapter 4).



Entry	Stannane	Cat.	Temp. / °C	Trace air[a]	Conv.[b] / %	Reaction colour[c]	Comments
1	*Z*	*cis*	60	no	10/14	yellow	
2	*Z*	*cis*	60	yes	15/18	black	
3	*Z*	*trans*	60	no	38	yellow	
4	*Z*	*trans*	60	yes	18	black	
5	*Z*	*cis*	60	no	22	brown	single crystals
6	*Z*	*cis*	60	yes	24	black	single crystals
7	*E*	*cis*	60	no	46	yellow	
8	*E*	*cis*	60	yes	26	black	
9	*E*	*trans*	60	no	98/88	yellow	
10	*E*	*trans*	60	yes	40/59	black	
11	*Z*	*cis*	70	no	36	yellow	
12	*Z*	*cis*	70	yes	37	black	
13	*Z*	*trans*	70	no	74	brown	
14	*Z*	*trans*	70	yes	50	black	
15	*Z*	*cis*	90	no	84	yellow	*Z:E* = 5.9:1[b]
16	*Z*	*cis*	90	yes	96	black	*Z:E* = 2.2:1[b]
17	*Z*	*trans*	90	no	96	yellow	*Z:E* = 7.7:1[b]
18	*Z*	*trans*	90	yes	94	black	*Z:E* = 1.6:1[b]

[a]'Trace air' refers to air exposure by removing the stopper of the Schlenk tube for 5 seconds with rapid stirring at the start of the reaction. [b]As judged by ^{1}H NMR spectroscopy. Separate repeats separated by a solidus (/). [c]Colour of the reaction mixture as judged by eye after 3 h.

Table 27 Data for reactions Stille reactions using catalyst **23** carried out in DMF (Chapter 4).



Entry	Stannane	Cat.	Temp / °C	Trace air[a]	Conv.[b] / %	Reaction colour[c]
1	*Z*	*cis*	60	no	74	yellow
2	*Z*	*cis*	60	yes	96	black
3	*Z*	*trans*	60	no	66/83	yellow
4	*Z*	*trans*	60	yes	92/97	yellow
5	*E*	*trans*	60	no	100	yellow
6	*E*	*trans*	60	yes	100	black
7	*Z*	*cis*	90	no	96	yellow
8	*Z*	*cis*	90	yes	88	black
9	*Z*	*trans*	90	no	94	yellow
10	*Z*	*trans*	90	yes	99	black
11	*E*	*cis*	90	no	99	yellow
12	*E*	*cis*	90	yes	100	black
13	*E*	*trans*	90	no	97	yellow
14	*E*	*trans*	90	yes	97	black
15	*Z*	*trans*	RT	no	0	pale yellow
16	*Z*	*trans*	RT	yes	0	pale yellow
17	*Z*	Pd-NPs[d]	RT	no	96	yellow
18	*Z*	Pd-NPs[d]	60	no	94	black

[a] 'Trace air' refers to air exposure by removing the stopper of the Schlenk tube for 5 seconds with rapid stirring at the start of the reaction. [b]As judged by ^{1}H NMR spectroscopy. Separate repeats separated by a solidus (/). [c]Colour of the reaction mixture as judged by eye after 3 h. [d]Pre-synthesised DMF-stabilised palladium nanoparticles.

Appendix 3: X-Ray Diffraction Data

Crystallographic data for compound 135

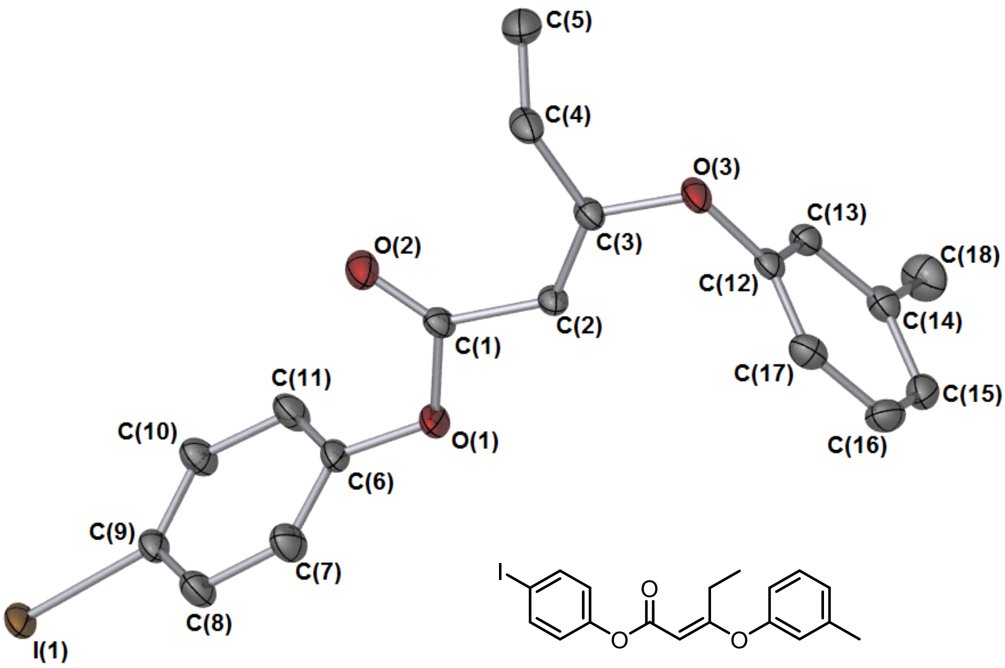


Figure 44 Single crystal X-ray diffraction structure of compound **135**. Hydrogen atoms removed for clarity. Thermal ellipsoids shown with probability of 50%.

Table 28 Crystal data and structure refinement for ijsf1205 (compound **135**).

Identification code	ijsf1205
Empirical formula	$C_{18}H_{17}IO_3$
Formula weight	408.22
Temperature/K	110.00(10)
Crystal system	triclinic
Space group	*P*-1
a/Å	6.3811(3)
b/Å	8.7585(4)
c/Å	15.2319(8)
α/°	76.494(4)
β/°	85.421(4)
γ/°	87.858(4)
Volume/Å^3	824.96(7)
Z	2
ρ_{calc}mg/mm^3	1.643
m/mm^{-1}	1.950
F(000)	404.0
Crystal size/mm^3	0.2433 × 0.1237 × 0.0831
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection	6.06 to 70.2°
Index ranges	$-10 \leq h \leq 10$, $-14 \leq k \leq 10$, $-21 \leq l \leq 24$
Reflections collected	11726
Independent reflections	7286[R(int) = 0.0238]
Data/restraints/parameters	7286/0/201
Goodness-of-fit on F^2	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0334, wR_2 = 0.0734
Final R indexes [all data]	R_1 = 0.0411, wR_2 = 0.0781
Largest diff. peak/hole / e Å^{-3}	1.61/−1.01

Crystallographic data for compound trans-*229 (CCDC 1036905)*

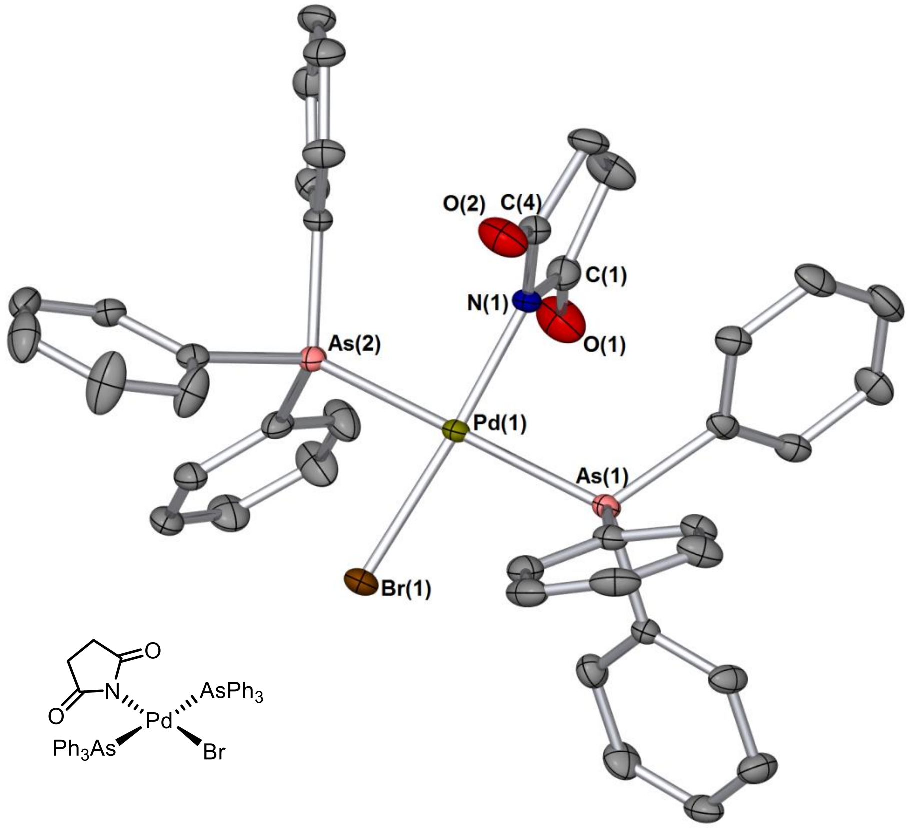


Figure 45 Single crystal X-ray diffraction structure of complex **229**. Hydrogen atoms removed for clarity. Thermal ellipsoids shown with probability of 50%. Selected bond lengths (Å): Pd(1)–As(1): 2.4229(4), Pd(1)–Br(1): 2.4338(4), Pd(1)–As(2): 2.3914(4), Pd(1)–N(1): 2.025(2). Selected bond angles (°): N(1)–Pd(1)–As(1): 90.69(7), As(1)–Pd(1)–Br(1): 92.969(13), Br(1)–Pd(1)–As(2): 87.471(13).

Table 29 Crystal data and structure refinement for ijsf1401 (compound **229**).

CCDC Number	CCDC 1036905
Identification code	ijsf1401
Empirical formula	$C_{40}H_{34}As_2BrNO_2Pd$
Formula weight	896.83
Temperature/K	110.05(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	12.2363(2)
b/Å	15.6103(3)
c/Å	19.0632(3)
α/°	90
β/°	105.4121(17)
γ/°	90
Volume/$Å^3$	3510.35(11)
Z	4
ρ_{calc}mg/mm^3	1.697
m/mm^{-1}	3.574
F(000)	1776.0
Crystal size/mm^3	0.2713 × 0.1255 × 0.0375
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection	5.664 to 60°
Index ranges	$-17 \leq h \leq 13$, $-19 \leq k \leq 21$, $-26 \leq l \leq 25$
Reflections collected	18231
Independent reflections	10230 [R_{int} = 0.0319, R_{sigma} = 0.0582]
Data/restraints/parameters	10230/0/424
Goodness-of-fit on F^2	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0405, wR_2 = 0.0798
Final R indexes [all data]	R_1 = 0.0699, wR_2 = 0.0933
Largest diff. peak/hole / e $Å^{-3}$	0.91/−0.99

Crystallographic data for compound 283

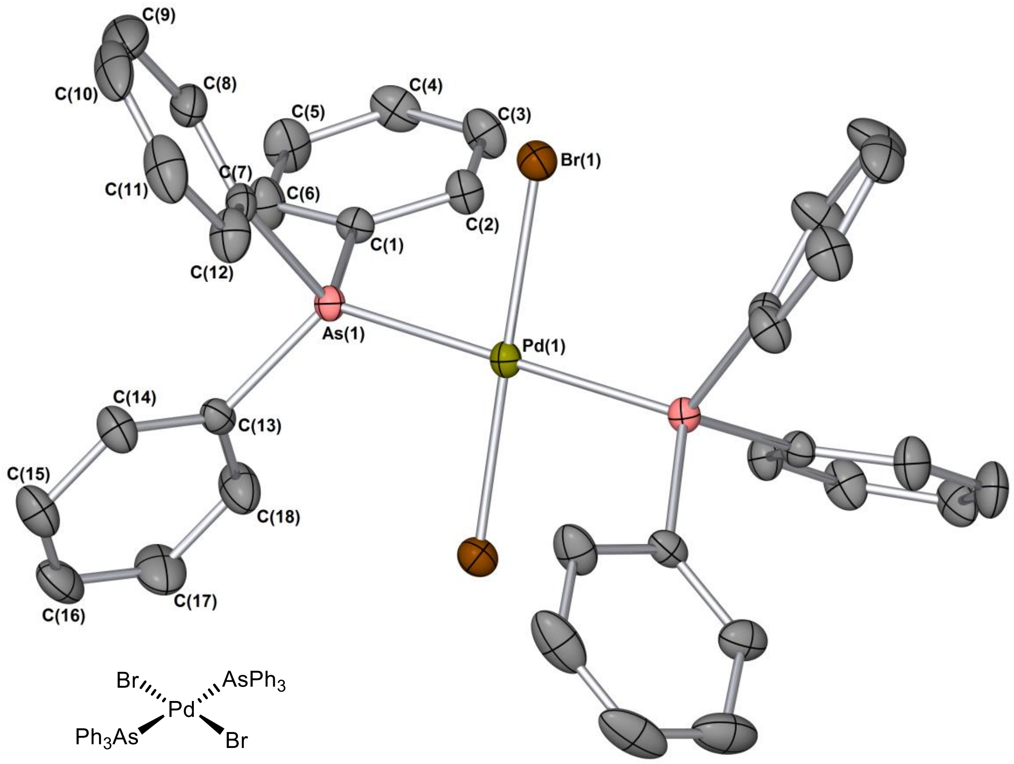


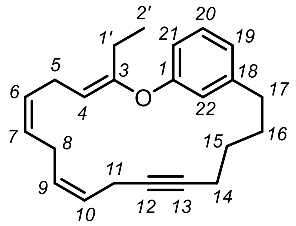
Figure 46 Single crystal X-ray diffraction structure of compound **283**. Hydrogen atoms and co-crystallised $CHCl_3$ removed for clarity. Thermal ellipsoids shown with probability of 50%. Selected bond lengths (Å): Pd(1)–As(1): 2.4043(3), Pd(1)–Br(1): 2.4180(3).

Table 30 Crystal data and structure refinement for ijsf1505 (compound **283**).

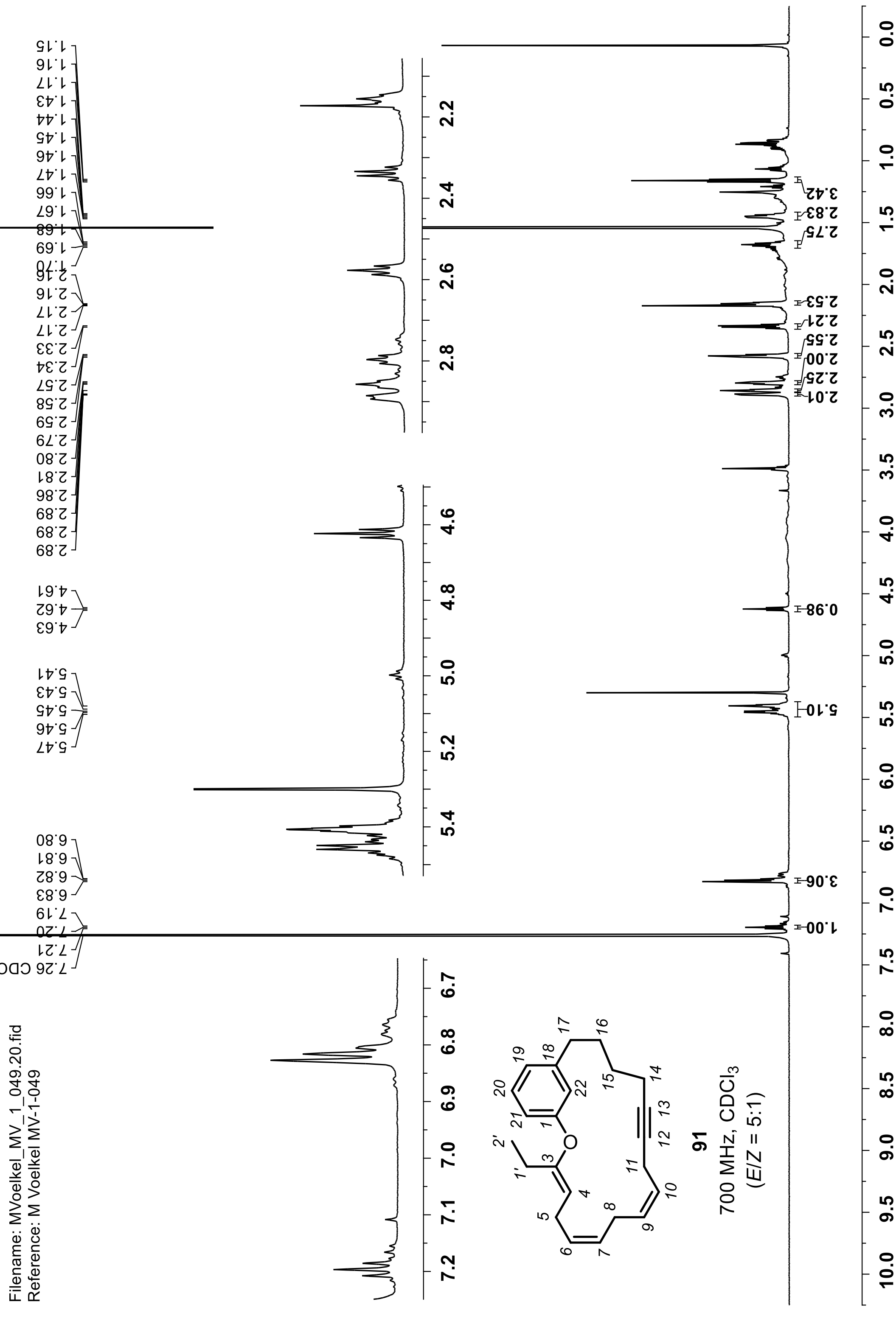
Identification code	ijsf1505
Empirical formula	$C_{37}H_{31}As_2Br_2Cl_3Pd$
Formula weight	998.03
Temperature/K	143(40)
Crystal system	monoclinic
Space group	*C*2/*c*
a/Å	12.2130(5)
b/Å	14.5533(5)
c/Å	20.4738(7)
α/°	90
β/°	91.371(3)
γ/°	90
Volume/Å^3	3637.9(2)
Z	4
ρ_{calc}mg/mm^3	1.822
m/mm^{-1}	4.759
F(000)	1944.0
Crystal size/mm^3	0.2041 × 0.1273 × 0.0804
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection	6.674 to 64.316
Index ranges	$-16 \leq h \leq 18$, $-21 \leq k \leq 18$, $-30 \leq l \leq 21$
Reflections collected	11411
Independent reflections	5772 [R_{int} = 0.0219, R_{sigma} = 0.0344]
Data/restraints/parameters	5772/0/222
Goodness-of-fit on F^2	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0320, wR_2 = 0.0672
Final R indexes [all data]	R_1 = 0.0531, wR_2 = 0.0784
Largest diff. peak/hole / e Å^{-3}	0.71/−0.90

Appendix 4: Spectral data for compound 91

Table 31 Table of correlations for compound **91**.

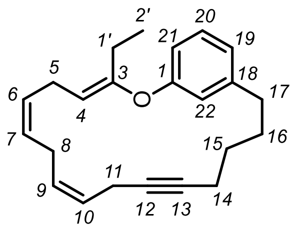


^{1}H NMR ($CDCl_3$, 700 MHz)							^{13}C NMR ($CDCl_3$, 175 MHz)	
No	**δ / ppm**	**Integral**	**M**	**COSY**	***J* / Hz**	**NOESY**	**δ / ppm**	**HMBC**
1	-	-	-	-	-	-	156.7	*4, 5, 20, 1′, 2′*
3	-	-	-	-	-	-	156.7	
4	4.62	1H	t	*5*	7.6	*5*	106.5	*5, 1′*
5	2.81–2.78	2H	m	*4, 6/7*	-	*4, 6/7, 1′*	24.9	*6/7*
6	5.43–5.38	1H	m	*5, 8*	-	*4, 5, 8*	128.6	*5*
7		1H					128.0	*5, 8*
8	2.86	2H	t	*6/7, 9/10*	5.6	*6/7, 9/10*	25.6	*6/7*
9	5.48–5.43	1H	m	*8, 11*	-	*8, 11*	124.7	*8, 11*
10		1H					130.0	*11*
11	2.89	2H	dt	*9/10, 14*	5.8, 2.3	*9/10*	17.2	-
12	-	-	-	-	-	-	78.4	*14*
13	-	-	-	-	-	-	79.9	*14, 15*
14	2.16	2H	tt	*11, 15*	7.0, 2.3	*15, 16, 17*	18.7	*15, 16*
15	1.48–1.41	2H	m	*14, 16*	-	*14, 16, 17*	28.0	*14, 16, 17*
16	1.71–1.64	2H	m	*15, 17*	-	*14, 15, 17*	30.5	*14, 15, 17*
17	2.58	2H	t	*16*	7.5	*14, 15, 16 19/21/22*	35.4	*15, 16*
18	-	-	-	-	-	-	143.9	*16, 17, 20*
19	6.83–6.81	1H	m	*17, 20*	-	*16,17, 20*	123.2	*17, 20, 21/22*
20	7.20	1H	t	*19/21/22*	7.7	*19/21/22*	129.6	*19/21/22*
21	6.83–6.81	1H	m	*17, 20*	-	*16, 17, 20*	117.5	*19/22*
22		1H					118.7	*17, 19/21*
1′	2.34	2H	q	*2′*	7.5	*5, 2′*	22.6	*5, 2′*
2′	1.16	3H	t	*1′*	7.5	*1′*	12.3	*1′*



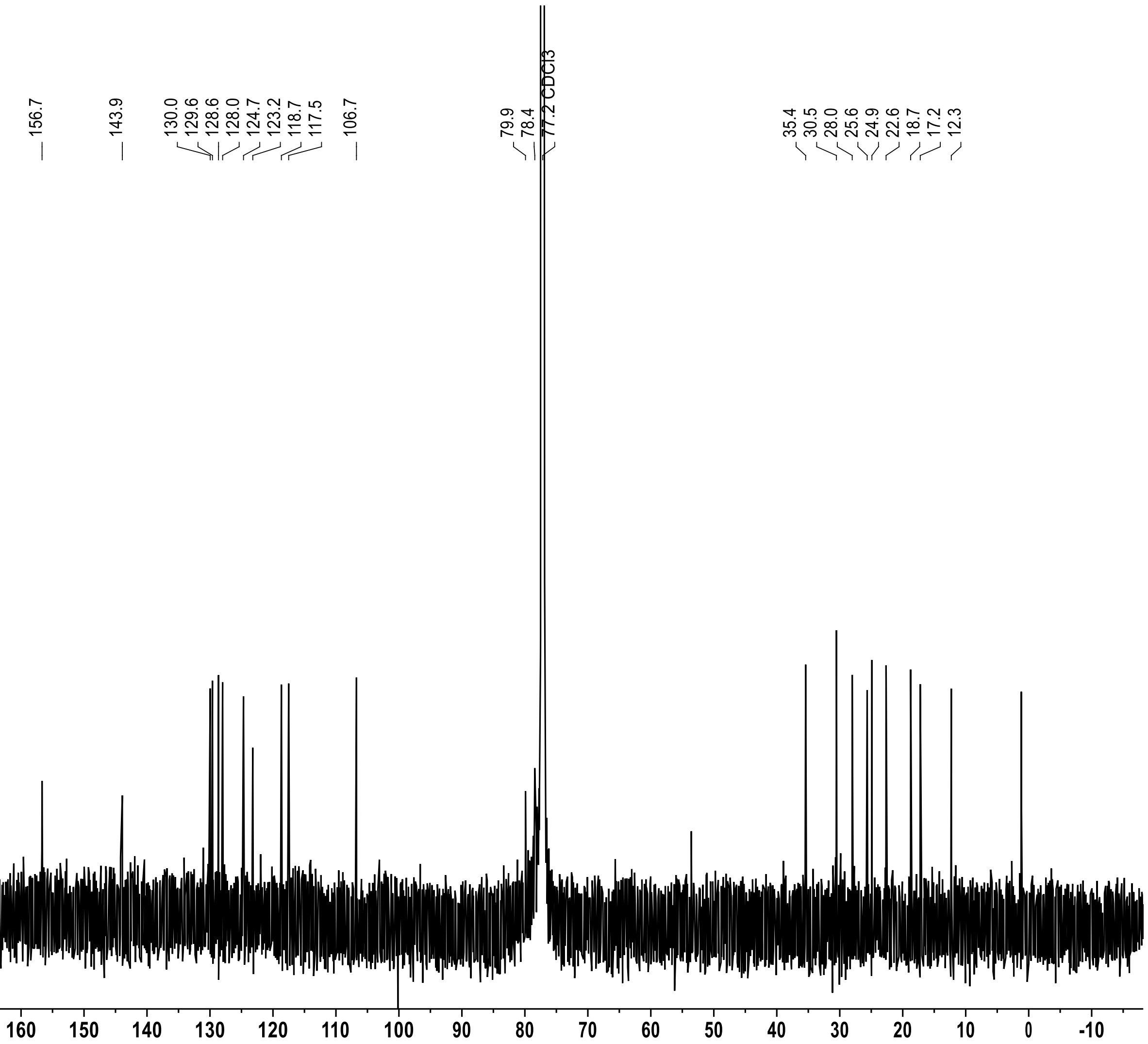
Filename: MVoelkel_MV_1_049.20.fid
Reference: M Voelkel MV-1-049
91
700 MHz, $CDCl_3$
(E/Z = 5:1)
7.26 CDCl3

Filename: MVoelkel_MV_1_049.11.fid
Reference: MV-1-049



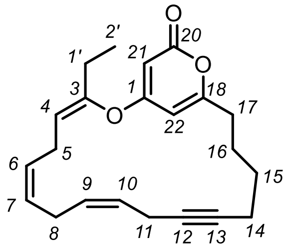
91

175 MHz, $CDCl_3$

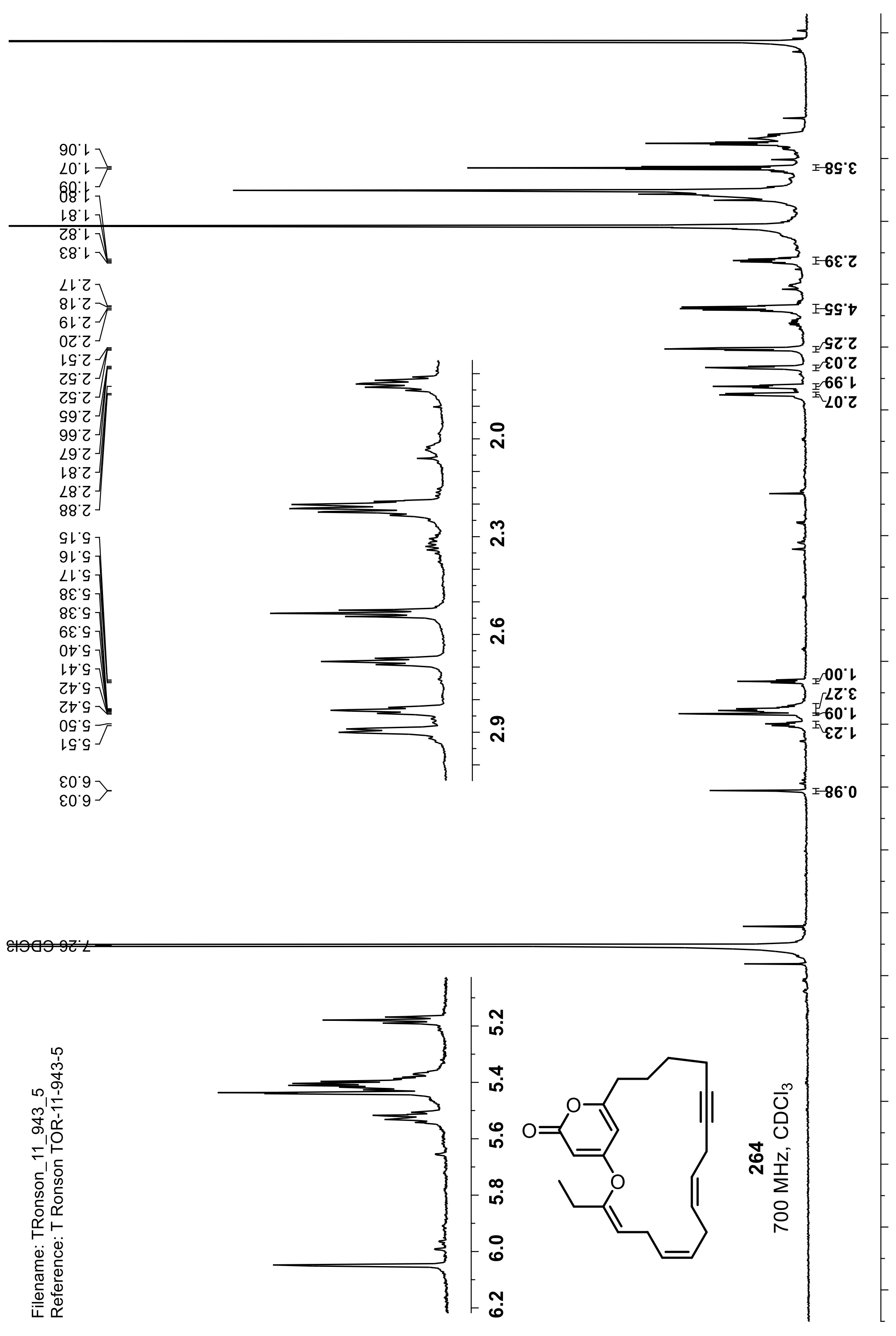


Appendix 5: Spectral data for compound 264

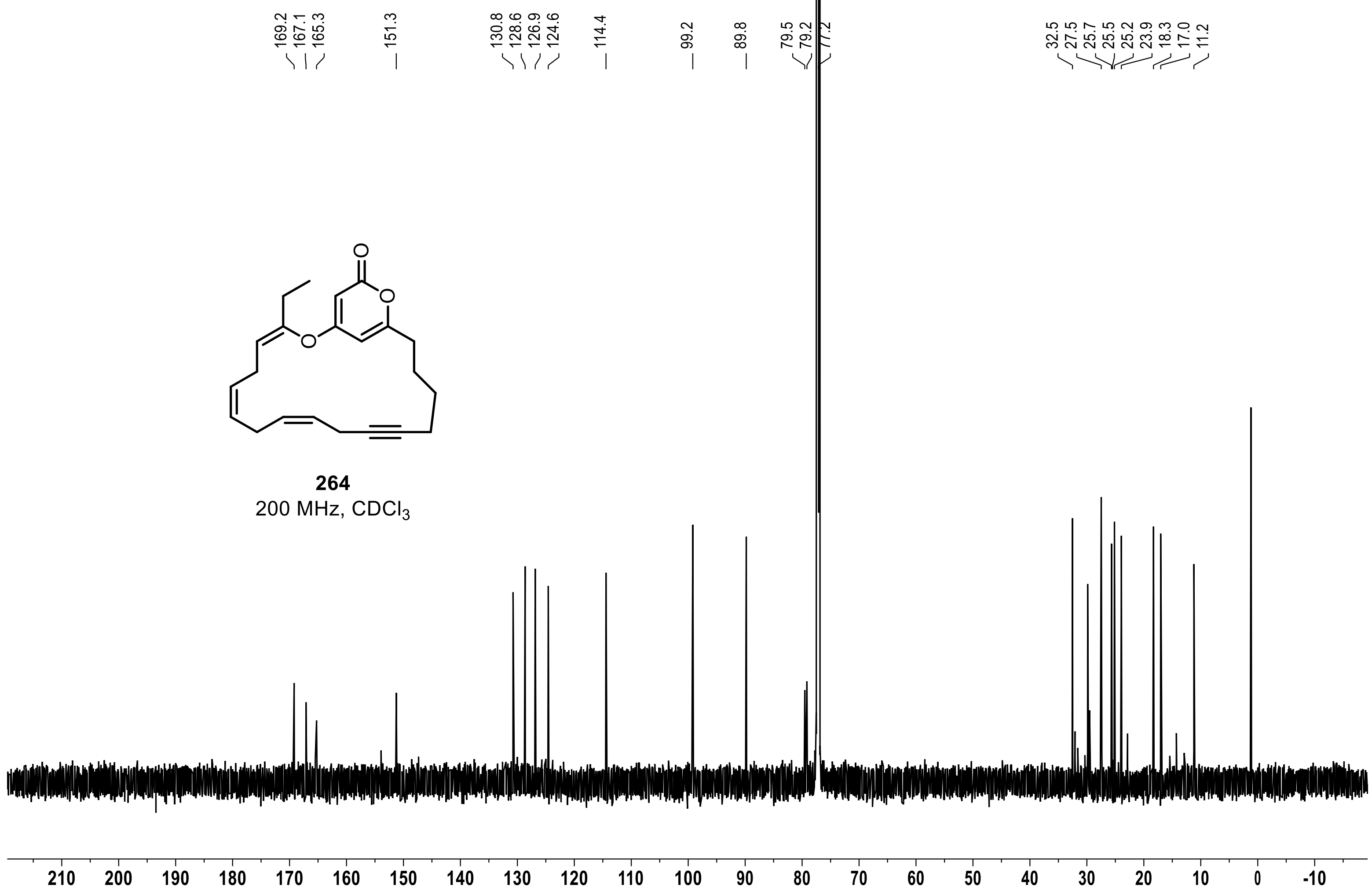
Table 32 Table of correlations for compound **264**.



^{1}H NMR ($CDCl_3$, 700 MHz)						^{13}C NMR ($CDCl_3$, 200 MHz)	
No.	**δ / ppm**	**Integral**	**M**	**COSY**	***J* / Hz**	**δ / ppm**	**HMBC**
1	-	-	-	-	-	165.3	*21*
3	-	-	-	-	-	151.3	*4, 5, 1′, 2′*
4	5.16	1H	t	*5, 1′*	7.5	114.4	*5, 1′*
5	2.66	2H	t	*6/7, 1′*	7.1	23.9	-
6	5.41–5.34	1H	m	*5, 8*	-	126.9	*8, 5*
7		1H				128.6	*8, 5, 11*
8	2.81	2H	t	*6/7, 9*	6.1	25.5	*9, 10, 11*
9	5.41–5.34	1H	m	*8, 10*	-	130.8	*11, 8*
10	5.54–5.47	1H	m	*11, 9*	-	124.6	*11, 8*
11	2.87	2H	d	*10, 14*	7.6	17.0	*9*
12	-	-	-	-	-	79.2	*11*
13	-	-	-	-	-	79.5	*14, 15*
14	2.23–2.16	2H	m	*11, 15*	-	18.3	*15, 16*
15	1.62–1.53	2H	m	*14, 16*	-	27.5	*14, 16, 17*
16	1.81	2H	p	*15, 17*	7.0	25.2	*14, 15, 17*
17	2.51	2H	t	*16, 22*	6.8	32.5	*15, 16*
18	-	-	-	-	-	167.1	*16, 17, 22*
20	-	-	-	-	-	169.2	*21*
21	5.42	1H	d	*22*	2.2	89.8	*22*
22	6.01	1H	d	*17, 21*	2.2	99.2	*17, 21*
1′	2.23–2.16	2H	m	*5, 2′*	-	25.7	*2′*
2′	1.07	3H	t	*1′*	7.4	11.2	*1′*


Filename: TRonson_11_943_5
Reference: T Ronson TOR-11-943-5
264
700 MHz, CDCl3
7.26 CDCl3
6.03
6.03
5.51
5.50
5.42
5.42
5.41
5.40
5.39
5.38
5.38
5.17
5.16
5.15
2.88
2.87
2.81
2.67
2.66
2.65
2.52
2.52
2.51
2.20
2.19
2.18
2.17
1.83
1.82
1.81
1.80
1.09
1.07
1.06
0.98
1.23
1.09
3.27
1.00
2.07
1.99
2.03
2.25
4.55
2.39
3.58
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
6.2
6.0
5.8
5.6
5.4
5.2
2.9
2.6
2.3
2.0

Filename: tomronson_060515.802.fid
Reference: T Ronson TOR-11-943-5



264
200 MHz, $CDCl_3$

Appendix 6: UV–Visible Spectroscopy Data

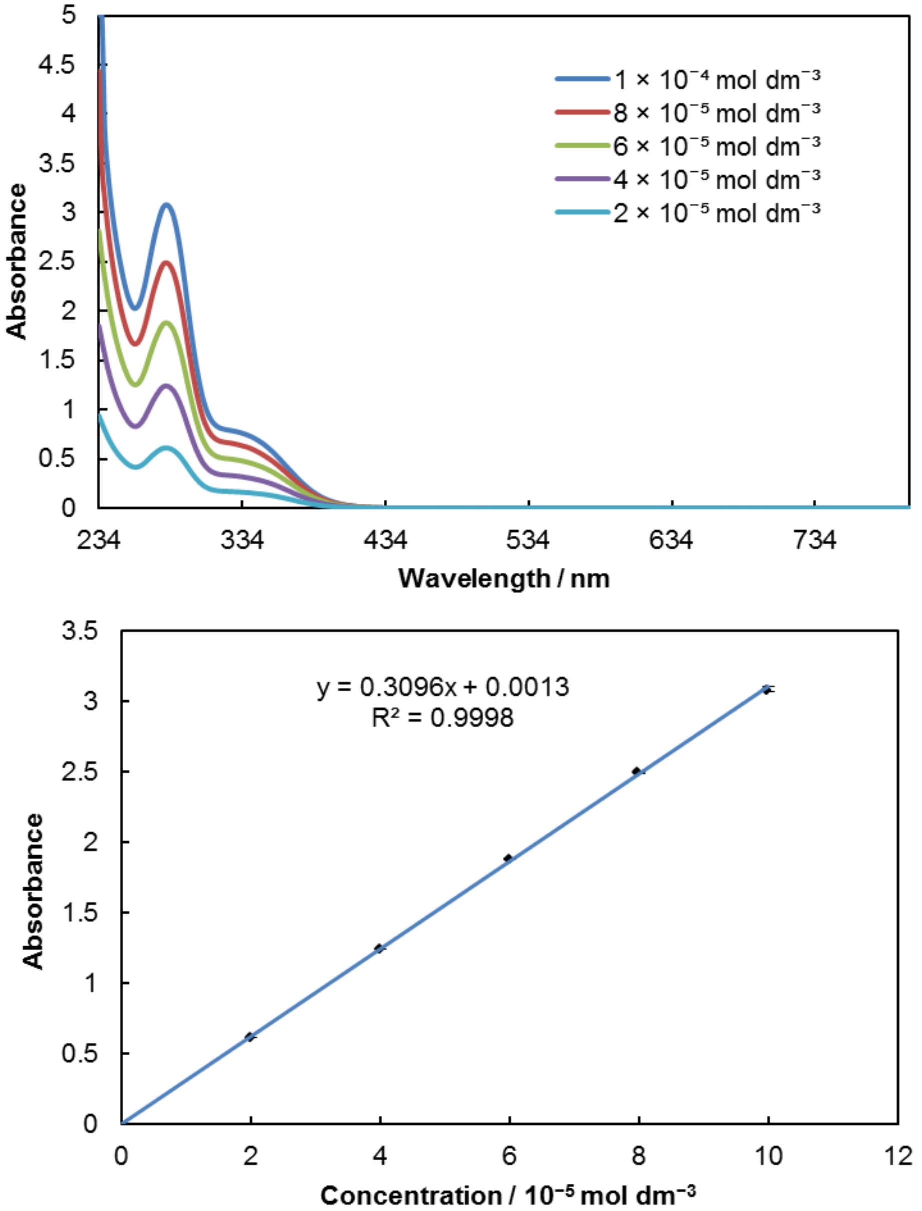
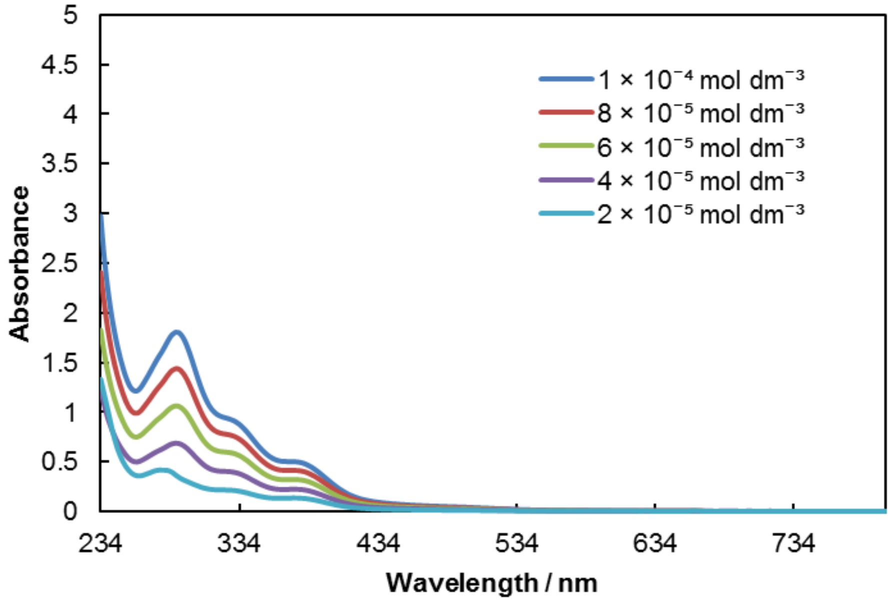


Figure 47 UV–visible spectroscopy data for compound *cis*-**23**.



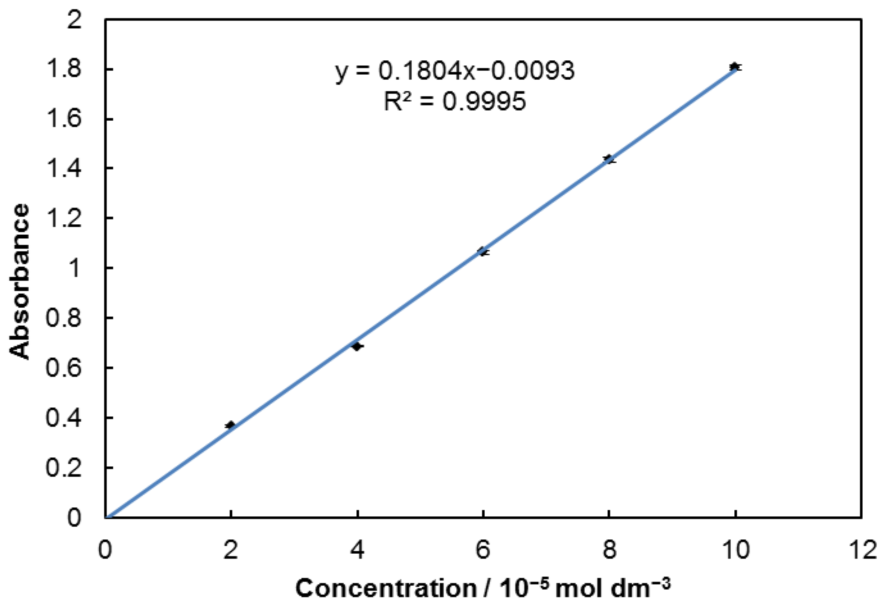
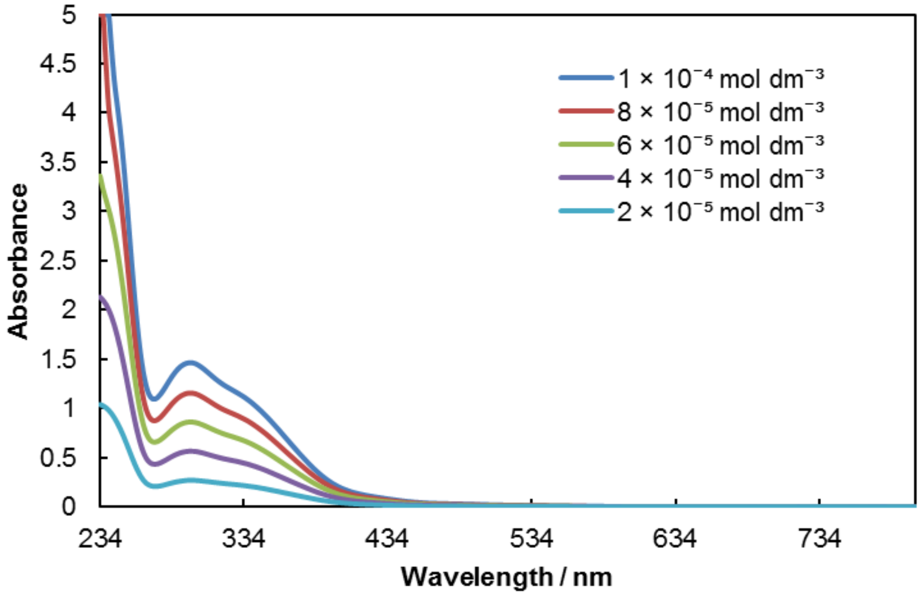


Figure 48 UV–visible spectroscopy data for compound **229**.



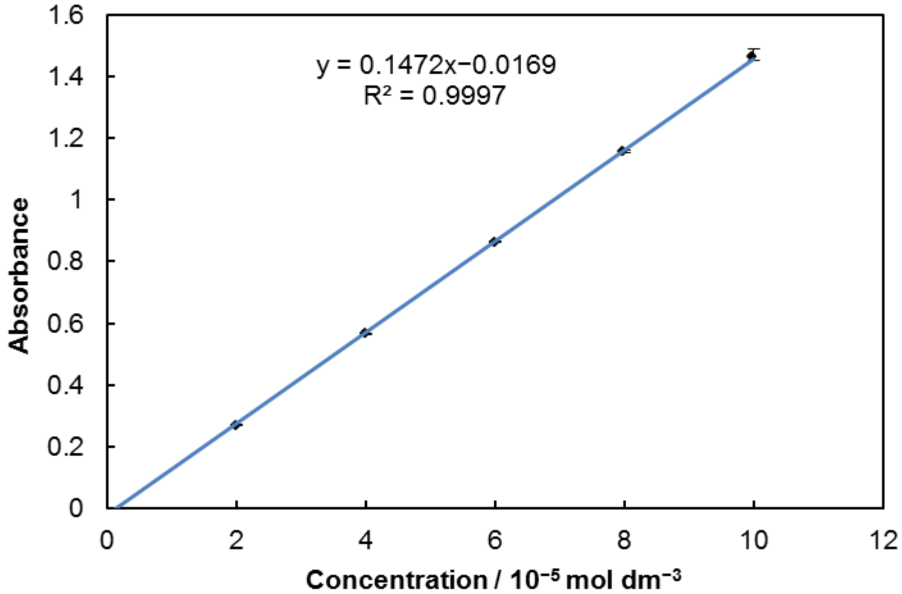


Figure 49 UV–visible spectroscopy data for compound **282**.

Abbreviations

ABCat	*trans*-(P,N)-[PdBr-(μ-C_5H_4N-C^2,N)(PPh_3)]$_2$
Ac	acetyl
AIBN	azobisisobutyronitrile
APCI	atmospheric pressure chemical ionisation
aq.	aqueous
ATR	attenuated total reflectance
Bn	benzyl
Bu	butyl
C, *c*.	concentration
c.	concentrated
cat.	catalyst, catalytic
cod	1,5-cyclooctadiene
conv.	conversion
COSY	correlation spectroscopy
Cp	cyclopentadienyl
Cy	cyclohexyl
dba	dibenzylideneacetone
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
dec.	decomposition
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobuylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine

DMAP	dimethylaminopyridine
DMC	2-chloro-1,3-dimethylimidazolinium chloride
DMEAD	di-2-methoxyethyl azodicarboxylate
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
DPEphos	(oxydi-2,1-phenylene)bis(diphenylphosphine)
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
EI	electron ionisation
EM	effective molarity
Enz	enzyme
eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
EXAFS	extended X-ray absorption fine structure spectroscopy
FGI	functional group interconversion
Fu	furyl
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	hexamethyldisilazane, hexamethyldisilazide
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence spectroscopy
i-	*iso*-
Imid.	imidazole

IPr	1,3-bis(2,6-triisopropylphenyl)imidazol-2-ylidene
IR	infrared
isol.	isolated
JohnPhos	(2-biphenyl)di-*tert*-butylphosphine
L	ligand
LIFDI	liquid introduced field desorption ionisation
lit.	literature
[M]	metal
m-	*meta*-
Me	methyl
Mes	mesityl
MOM	methoxymethyl
M.P.	melting point
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	molecular sieves
Ms	methanesulfonic, methanesulfonyl
Mw	molecular weight
n-	*normal*
NBS	*N*-bromosuccinimide
NBSac	*N*-bromosaccharin
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Np	neopentyl
N. R.	no reaction
Nu	nucleophile

nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
[P]	protecting group
p-	*para*-
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PdNPs	palladium nanoparticles
Ph	phenyl
Pin	pinacol ester
Piv	pivaloyl
PLA_2	phospholipase A_2
ppm	parts per million
Pr	propyl
PVP	(poly)vinylpyrrolidinone
pyr.	pyridine
Q-Phos	1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene
quant.	quantitative yield
rel.	relative
R_f	retention factor
RCAM	ring-closing alkyne metathesis
RCM	ring-closing alkene metathesis
RT	at ambient temperature
SEM	[2-(trimethylsilyl)ethoxy]methyl
SM	starting material
succ	succinimide
t-	*tertiary*
TBAC	tetra-*n*-butylammonium chloride

TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Temp.	temperature
TES	triethylsilyl
TEM	transmission electron microscopy
Tf	triflic, trifluoromethanesulfonic
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N′*,*N′*-tetramethylethylenediamine
TMS	trimethylsilyl
tol	toluene
TPAP	tetrapropylammonium perruthenate
Ts	tosyl, toluenesulfonyl
UV	ultraviolet
w.r.t.	with respect to
X	leaving group
XANES	X-ray absorption near edge spectroscopy
XAS	X-ray absorption spectroscopy
X-Phos	2-(dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl
xs.	in excess

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